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THE WAR COMES HOME TO PEDIATRICS

Presidential Address

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AT A recent staff meeting in Rochester a commander in the Navy who had served as a psychiatrist throughout the war both at the front and in large base hospitals showed the Navy films on "Combat Fatigue" and "Irritability." At the end of the conference after the lights were on, he said in effect: "We have shown you these films to demonstrate the pathogenesis of many instances of war neurosis and to show you how we try to treat them. But one thing which has not been mentioned stands out in my experience. Each one of these mentally ill men had in his background an underlying emotional insecurity which dated back to family situations, often into babyhood. If we are going to prevent psychoneurosis in future conflicts, we have got to begin in earliest infancy to breed into our babies a basic sort of security which we have failed to give them in the past."

This same sort of statement has been made over and over by psychiatrists in the past few years, and in a way such statements throw the problem of mental hygiene into the laps of pediatricians as the only physicians who routinely see little babies.

We are put into a position in which it is necessary for us to make up our minds as to whether we, as pediatric specialists, are going to continue our traditional policy of focusing our attention predominantly on the job of more expert care of physically sick children or whether we are going to face with the same enthusiasm newer and more untried fields in the area of mental health.

For more than half a century the specialty of pediatrics has distinguished itself by heading what was probably the most successful attack ever made on the problem of human mortality. So successful was this effort that it has been the major factor in the recent trend toward increased human longevity. Child mortality rates have been reduced to a point which fifty years ago would have appeared fantastic. It is useless to list the long roster of diseases which have come under approximate

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control, for you know them all well. This campaign has been won by the hard work of generations of physicians devoted to a great cause.

And this effort is by no means finished. The time has not yet arrived when we can mop our brows in contentment and rest from our labors in the healing of physical ailments. New diseases plague our complacency: virus infections, toxoplasmosis, histoplasmosis and what not are just around the corner. New drugs, bewildering in their complexity, number and possibilities, challenge us to further conquest in what were thought to be incurable conditions.

And we still have that least known of all areas, the house of the newborn, to put in order. If anything can be done to make an appreciable reduction in neonatal deaths, another great stride will have been taken toward reducing human mortality rates. The subjects of prevention of premature birth, of congenital defects and of pulmonary atelectasis are but a few of the wide open fields for investigation and for therapy. More exact knowledge of human beings at this age is badly needed, and when it is gained it will surely pay dividends in lives to be saved.

I mention these matters concerned with the investigation of and mastery of physical ailments because I have considerable sympathy with the harassed physican who, on hearing a talk on mental hygiene or the psychology of infants, shakes his head in bewilderment and says, "But I'm so busy taking care of sick children that I don't have time for their mental health."

This attitude is understandable, and a fairly good case can be made out for the physician well trained in pathology, chemistry, physiology and pediatrics who decides to continue to be lured on by the promise of triumph over physical disease. One cannot quarrel with such a person. There is still a big job to be done in this strictly medical area, and some one has to do it.

But, on the other hand, viewed from the broader field of pediatrics as the study of the whole child, such an ideal is not enough. It is one-sided and ignores areas of equal magnitude which involve questions of great medical and social importance. Officers in the armed forces are as keyed up over psychoneurosis as they are over the results of burns and gunshot wounds, and we are at least implicated in the former. Moreover, many seemingly physical ills are so entangled with emotional connotations that it is impossible to separate the two concepts in appraising an individual situation.

Every pediatrician with experience in active practice knows that he is asked as many—or more—questions about behavior and training of children as he is about tonsils, knock knees and measles, and the usual answers to the former questions have been built up over many years in a remarkably traditional manner. And, as we have given these more or less stereotyped answers, we have unwittingly reflected on them some

of the glamour derived from our phenomenal success in the scientific treatment of disease.

It seems to me that it is time for all of us to pause and investigate some of these answers to see if we have given them the same scientific tests of validity that we are accustomed to use in such matters as infectious disease, endocrinology and nutrition.

Shall a crying baby be soothed, or shall he be allowed to cry it out routinely? Shall a baby be trained at 6 weeks for bowel control? Shall we force a baby to eat a prescribed amount of formula; shall we restrict his intake, or shall we allow his natural appetite full range? When and how long should a baby sleep? Should an infant be trained to play alone? If so, at what age? When shall we expect obedience? When shall we expect self discipline? What are the effects of corporal punishment, of scolding? What shall we do about thumb sucking, about masturbation, about tantrums? What shall we do about the sex drive of adolescents?

The traditional answers which pediatricians have given to these questions have, I believe, a decidedly Teutonic origin. This is quite natural because we learned our early pediatrics, to a large extent, from German and Austrian teachers. But the results that we have had in personality development have not, according to our best information, been anything like as successful as have been the results of our curative medicine. Mental disease is admittedly increasing, and the war statistics are alarming at the same time that mortality rates decrease.

It seems to me quite clear why there should be so great a divergence of results from the same teachers in these two areas, physical and emotional therapy. The instruction in curative medicine was based on rapidly and concurrently developing scientific knowledge about physical disease. However, the instruction on the psychologic side preceded the acquisition of knowledge of normal growth and development, on which any logical regimen for conduct must be based. How could one possibly answer scientifically any of the questions just mentioned without understanding the facts of development which underlie them? In the early days of pediatrics we simply didn't know these basic facts, and we were led away by the voice of authority into mistaken conclusions, which in the light of the science of growth and development will have to be critically reviewed. Thus only can we give scientifically sound answers to the important issues raised.

Here we are, a selected group of pediatricians, most of us teachers of medical students. Shall we hew to the line and continue our attempts to conquer physical disease alone, or shall we face the newer issue, search for knowledge and skills in the mental and emotional fields and incorporate what we learn in our teaching to students so that they can care for the whole child?

This venture into the field of functional growth and development, mental hygiene or behavior problems, or whatever we choose to call it, will not be a journey into entirely new areas. Rather, it will mean a reorientation toward an aspect of pediatrics which in the past has been cared for less scientifically than the rest of our work has been.

Practically all the behavior difficulties in childhood have their origin in conflicts arising out of the differences between the nature of the child and the rules set up in his environment to govern his behavior.

In many instances troubles start because those who care for children have not learned to expect them to act their age. It seems almost axiomatic that we should not expect behavior for which a child's growth and development have not yet prepared him. A thorough knowledge of developmental progress is, therefore, necessary before a pediatrician has the factual background on which to base his advice to parents about such important matters as basic habit formation, infantile crying and even the problems of adolescence. How can a physician advise as to habits of urinary control unless he learns the laws of growth which apply to such control? How can he interpret the crying of the newborn infant unless he understands the stage of mental and emotional growth of such babies? And where can he obtain such information in our medical curriculums? How often does the pediatric student have an opportunity for clinical experience in such problems?

In many cases difficulties arise because adults do not allow children to live up to the capabilities laid down by their growth. This is particularly evident in the second year of life, when an infant strives with all his physical, mental and emotional power to get functional control over the capabilities that have developed in his first year. Gradually the "do it myself" motif is built up as the baby struggles with his neuromuscular control. And, as if to confound his growth and development completely, adults respond with a crescendo of "no, no." Many children are labeled "bad" simply because parents do not allow them to do the things which are dictated to them by inherent growth drives. The fact that many of these commands of "no, no" are necessary from the standpoint of safety does not relieve the physician of his responsibility to explain such situations to parents. By these explanations he can make the rebellious toddler seem more reasonable than bad.

Again, problems arise out of pediatricians' interpretation of the mental and emotional status of very young infants. Specifically, I am thinking of the so-called spoiling of infants less than 3 months of age. It is well established that at this tender age an infant is just beginning to achieve a very small amount of voluntary control over his activities and that this is limited to the region of the head and neck. He is still under the domination of his automatic emotional safety controls.

It does not seem an overstatement to say that pediatricians have generally taught the thesis that responding to a baby's cry of need at this age would train him to cry for attention and would, in other words, spoil him. This seems to me incomprehensible if the facts of the matter are studied. In the first place, neonatal crying is entirely reflex and is used as a signal of need. Obviously it should be responded to intelligently, in the interest of safety if for no other reason. In the second place, infants at this age are incapable of the mature mental processes necessary for the production of spoiling through indulgence. I might add, in the third place, that after twenty-five years of active practice with infants, in which I have deliberately advocated sympathetic response to a small infant's cries, including the liberal use of rocking chairs, I have yet to find a mother who felt that this method spoiled her baby; on the contrary, most mothers felt that it helped to make the baby more responsive.

I would suggest that this is an extremely important matter, which is subject to the experimental approach, and that impartial observers should face the problem on a research basis. We are attempting to get some accurate information on the subject in the Rochester Child Health Project.

It would be possible to go on indefinitely illustrating the mental health or emotional adjustment aspects of pediatrics, but no further end would be served. However, I feel that it should be reemphasized that these problems we are facing are not those of personal opinion any longer—that the science of growth and development has given us a method by which we can prove or disprove the advisability of our technics which govern child manners and adjustment to civilized mores. As scientifically oriented physicians, the least we can do is to investigate the facts; the most we can do is to try to modify the mores to fit the normal abilities of children.

But the whole subject needs most of all the diligent and earnest application of scientific fact finding in order to live up to our past performances in child care. In this way only can we answer the challenges posed by war experience with emotionally disturbed soldiers.

RESISTANCE OF COTTON RATS TO THE VIRUS OF POLIOMYELITIS

As Affected by Intake of Certain Purified Vitamins and by Sex

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DETROIT

A NUMBER of clinical studies have indicated that victims of the virus of poliomyelitis are apparently the healthier, the better nourished and the more robust members of the family. Since, among other factors, an adequate intake of vitamins is a necessary prerequisite for health, it was thought advisable to determine whether or not an increased intake of vitamins would influence the susceptibility of the host to the virus.

For this purpose a number of experiments were designed to test the effects of hypervitamin diets and of sex on the susceptibility and on certain immunologic responses of cotton rats to the virus of poliomyelitis. The present communication records the results of this investigation.

MATERIALS

The Armstrong-Lansing strain of the virus of poliomyelitis which has been adapted to the cotton rat was employed in these studies. The unfiltered, lightly centrifuged suspensions of the virus were prepared exclusively from the brain stems and spinal cords of paralyzed cotton rats. The infected brain stems and spinal cords were stored in buffered glycerin at 5 C. for a period not exceeding two months.

The cotton rats employed in these studies were obtained from the Michigan Department of Health Laboratories.

The basic portion of the diet fed to the experimental and to the control animals consisted of the following substances: dextrose, 750 Gm.; sucrose, 4,350 Gm.; casein, 1,350 Gm.; hydrogenated cottonseed oil, 600 Gm.; U. S. P. salt mixture no. 2, 300 Gm., and cod liver oil (Mead, Johnson and Company), 150 Gm.

In the diet fed to the controls, the following quantities of purified vitamins were added to each 7,500 Gm. of the basic portion of the diet noted above: alpha tocopherol, 0.19 Gm. (dissolved in 19 cc. of ethyl laurate); thiamine, 0.06 Gm.; riboflavin, 0.12 Gm.; pyridoxine, 0.9 Gm.; calcium pantothenate, 0.075 Gm.; choline, 1.2 Gm.; ascorbic acid, 0.375 Gm.; nicotinic acid, 0.15 Gm.; carotene, 0.0045 Gm. (90 per cent beta and 10 per cent alpha, dissolved in 4.5 cc. of corn oil); inositol, 0.075 Gm., and irradiated ergosterol, 0.1 cc. (400,000 Steenbock units of vitamin D per cubic centimeter).

The hypervitamin diet was prepared by adding the following quantities of

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purified vitamins to each 7,500 Gm. of the basic portion of the diet noted: alpha tocopherol, 1.9 Gm. (dissolved in 185 cc. ethyl laurate); thiamine, 0.6 Gm.; riboflavin, 1.2 Gm.; pyridoxine, 9 Gm.; calcium pantothenate, 0.75 Gm.; choline, 12 Gm.; ascorbic acid, 3.75 Gm.; nicotinic acid, 1.5 Gm.; carotene, 0.045 Gm. (90 per cent beta and 10 per cent alpha, dissolved in 45 cc. corn oil); inositol, 0.75 Gm., and irradiated ergosterol, 1.0 cc. (400,000 Steenbock units of vitamin D per cubic centimeter). Thus, it can be seen that the hypervitamin diet contained approximately ten times the quantity of purified vitamins [1] that was present in the control diet.

EXPERIMENTAL PROCEDURE

The cotton rats were weaned at 25 days of age and divided according to sex. The animals of each sex were fed the laboratory stock diet (Rockland Farms rat pellets) until they were 46 days of age. At this time one half of the cotton rats of each sex were fed the control diet. The remaining animals were fed the hypervitamin diet. Thus, the animals were divided into two groups of approximately equal numbers as follows: Group 1 contained the control males and the control females, and group 2 the males and females on the hypervitamin diet. It was felt that this grouping would demonstrate differential susceptibility and immunologic response dependent on sex or nutrition.

The controls and the animals fed the hypervitamin diet, both of which were fed their particular diet *ad libitum,* thrived, presented no consistent abnormalities and exhibited no particular susceptibility to intercurrent infections. The daily consumption of food by the animals on the hypervitamin diet averaged 6.0 Gm., whereas that by the controls averaged 6.6 Gm. We were unable to determine any differences in the animals of these two groups after periods of feeding up to two months.

When each animal attained the age of 8 weeks, the virus of poliomyelitis was administered by one of several different experimental methods. In two experiments the virus was injected into the brain; in five it was injected or instilled into certain parts of the alimentary tract; in 2 it was instilled into different parts of the respiratory tract, and in the three remaining experiments it was administered through certain unusual portals.

With the exception of the animals in experiment 2, each cotton rat was returned to the laboratory stock diet (Rockland Farms rat pellets) on the sixteenth day after it had been inoculated with the virus.

Each animal was observed morning and evening for twenty-five days after administration of the virus. Any animal remaining free of symptoms during this interval was subjected to a three way reinoculation (0.1 cc. given intracerebrally, 0.5 cc. subcutaneously in the back and 0.06 cc. intranasally) with a 10 per cent suspension of the virus. Cotton rats remaining free of symptoms for another twenty-five days were subjected to a second three way reinoculation with the virus. Any animal failing to show symptoms of poliomyelitis after the first (or original) inoculation and two three way reinoculations with the virus was considered immune.

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1. The carotene used in these studies was furnished by the Research Laboratories of the S. M. A. Corporation, Chagrin Falls, Ohio. The following materials were supplied to us in generous quantity by Merck & Co., Inc., Rahway, N. J.: alpha tocopherol, thiamine, riboflavin, pyridoxine, calcium pantothenate, choline, ascorbic acid, nicotinic acid and inositol.

Each cotton rat said to have contracted poliomyelitis after its first inoculation with the virus, when the latter was administered by any route other than the intracerebral, satisfied the following four requirements: 1. Flaccid paralysis developed within twenty-five days after the virus was first administered, and observations of the animal at frequent intervals showed progressive paralysis. 2. Samples of the central nervous system showed histologic changes characteristic of anterior poliomyelitis. 3. The remaining portions of the central nervous system of the paralyzed cotton rat, when made up into a 10 per cent saline suspension and injected intracerebrally into 3 previously untreated cotton rats, reproduced symptoms of the disease in at least 1 of the 3 animals. 4. At least 1 of the 3 passage animals showed the histologic changes in its central nervous system which are characteristic of anterior poliomyelitis.

All animals which contracted poliomyelitis were permitted to live twenty-four hours after the paralysis was first observed. At the end of this period the extent of paralysis was recorded and the animal killed. The relative susceptibility of the cotton rats which contracted poliomyelitis after inoculation with the virus was judged from the number of extremities paralyzed and from the length of the incubation period (defined here as the number of days between the time of inoculation with the virus and the time the rat died or was killed). Any cotton rat in which paralysis developed in two or more extremities within fifteen days of an inoculation with the virus was considered to have no unusual resistance to the antigen.

RESULTS

Part 1. Comparative Response of Rats on the Hypervitamin Diet and of Control Rats Subjected to Intracerebral and to Three Way Inoculations with the Virus.

EXPERIMENT 1.—This experiment was performed in order to determine whether the vitamin intake of the host might influence its response to the virus of poliomyelitis when the latter is administered by a three way inoculation. Each cotton rat was subjected to a single three way inoculation (0.1 cc. given intracerebrally, 0.06 cc. intranasally and 0.5 cc. subcutaneously in the back) with a 10 per cent suspension of the virus. Table 1 summarizes the results of this experiment.

Of these animals, only 1 control male failed to contract the disease after its first inoculation with the virus. This animal also resisted two three way reinoculations with the virus. (This animal is not included in the summary presented in table 1).

EXPERIMENT 2.—This experiment was performed in order to determine whether the vitamin and/or the caloric intake of the host might influence its response to the virus of poliomyelitis when the latter is administered by intracerebral injection. The caloric intake of the animals in the two groups which were designated partial inanition males and partial inanition females, respectively, was limited to 50 per cent of the calories consumed by rats on the hypervitamin diet. The vitamin content of the diet fed to the partial inanition animals was adjusted so that each of these animals consumed daily the same quantity of vitamins as did the controls.

Each cotton rat was subjected to an intracerebral inoculation with 0.05 cc. of a 10^{-3} suspension of the virus. Table 2 summarizes the results of this experiment.

Table 3 summarizes the average incubation periods and the extent of paralyses of those animals which became paralyzed within fifteen days after the initial inoculation with the virus (see table 2).

TABLE 1.—*Results of Three Way Inoculation with the Virus*

Animals	Number of Animals	Average Incubation Period,* Days	Extent of Observable Paralysis, Extremities
Hypervitamin rats	40	3.50 (2-7)	2.10 (2-4)
Control rats	39	3.46 (2-7)	2.36 (2-4)
Males	39	3.60 (2-7)	2.15 (2-4)
Females	40	3.38 (2-7)	2.30 (2-4)
Hypervitamin males	20	3.80 (2-7)	2.10 (2-4)
Control males	19	3.37 (2-7)	2.21 (2-4)
Hypervitamin females	20	3.20 (2-7)	2.10 (2-4)
Control females	20	3.55 (2-7)	2.50 (2-4)

* Used in this communication to indicate the number of days which elapsed between the time of inoculation with the virus and the time the animal died or was killed.

TABLE 2.—*Results of Intracerebral Inoculation with the Virus*

Animals	Number of Animals	Paralyzed			Resistant to 2 Three Way Reinoculations
		Within Usual Incubation Period*	Only After Prolonged Incubation Period*	Only After First Reinoculation	
Hypervitamin rats	45	38	1	5	1
Control rats	45	39	1	3	2
Partial inanition rats	42	36	3	0	3
Males	67	56	3	7	1
Females	65	57	2	1	5
Hypervitamin males	24	18	1	4	1
Control males	22	18	1	3	0
Partial inanition males	21	20	1	0	0
Hypervitamin females	21	20	0	1	0
Control females	23	21	0	0	2
Partial inanition females	21	16	2	0	3

* Used in this communication to indicate the number of days which elapsed between the time of inoculation and the time the animal died or was killed. The term "usual incubation period" denotes paralysis in two or more extremities within fifteen days of an inoculation with the virus.

Part 2. Comparative Response of Rats on a Hypervitamin Diet and of Control Rats Subjected to Inoculations with the Virus into Different Parts of the Alimentary Tract.

EXPERIMENT 3.—This experiment was performed in order to determine whether the vitamin intake of the host might influence its response to the virus of poliomyelitis when the latter is administered as a contaminant of food. Each cotton rat devoured one brain stem and spinal cord which had been freshly removed from a cotton rat paralyzed with poliomyelitis. In order to maintain the relative intake of vitamins, the

brain stems and spinal cords which were fed to rats on the hypervitamin diet were in all cases removed from paralyzed rats on the hypervitamin diet. Similarly, the brain stems and spinal cords which were fed to control rats were in all cases removed from paralyzed rats which had been fed the control diet. Table 4 summarizes the results of this experiment.

TABLE 3.—*Average Incubation Periods and Extent of Paralyses of Animals Paralyzed Within Fifteen Days of the Initial Inoculation*

Animals	Number of Animals	Average Incubation Period,* Days	Extent of Observable Paralysis, Extremities
Hypervitamin rats	38	7.10 (2-13)	3.63 (2-4)
Control rats	39	7.89 (5-13)	3.69 (2-4)
Partial inanition rats	36	7.53 (4-11)	3.72 (2-4)
Males	56	7.79 (2-11)	3.73 (2-4)
Females	57	7.24 (4-13)	3.69 (2-4)
Hypervitamin males	18	7.44 (2-13)	3.72 (2-4)
Control males	18	7.67 (5-11)	3.67 (2-4)
Partial inanition males	20	8.20 (6-11)	3.80 (2-4)
Hypervitamin females	20	6.80 (4-9)	3.70 (2-4)
Control females	21	8.10 (5-13)	3.71 (2-4)
Partial inanition females	16	6.69 (4-11)	3.63 (2-4)

* Used in this communication to indicate the number of days which elapsed between the time of inoculation and the time the animal died or was killed.

TABLE 4.—*Results of Feeding One Brain and Spinal Cord to Each Rat*

Animals	Number of Animals	Paralyzed in 2 or More Extremities Within Usual Incubation Period			Resistant to 2 Three Way Reinoculations
		After Experimental Feeding	After First Reinoculation	After Second Reinoculation	
Hypervitamin rats	12	0	10	0	2
Control rats	12	0	12	0	0
Males	12	0	11	0	1
Females	12	0	11	0	1
Hypervitamin males	6	0	5	0	1
Control males	6	0	6	0	0
Hypervitamin females	6	0	5	0	1
Control females	6	0	6	0	0

EXPERIMENT 4.—This experiment was performed in order to determine whether the vitamin intake of the host might influence its response to the virus of poliomyelitis when the latter is injected beneath the pharyngeal mucosa. Each cotton rat was given a submucosal injection of 0.5 cc. of a 10 per cent suspension of the virus into each of the two regions which in certain animals other than cotton rats house the palatine tonsils. Table 5 summarizes the results of this experiment.

EXPERIMENT 5.—This experiment was performed in order to determine whether the vitamin intake of the host might influence its response to the virus of poliomyelitis when the latter is instilled into the upper

gastrointestinal tract. Each cotton rat was subjected to a single intragastric instillation of 1.0 cc. of a 10 per cent suspension of the virus administered by means of a stomach tube. Table 6 summarizes the results of this experiment.

EXPERIMENT 6.—This experiment was performed in order to determine whether the vitamin intake of the host might influence its response to the virus of poliomyelitis when the latter is instilled into the lower

TABLE 5.—*Results of Submucosal Injection of the Virus*

Animals	Number of Animals	Paralyzed in 2 or More Extremities Within Usual Incubation Period			Resistant to 2 Three Way Reinoculations
		After Experimental Inoculation	After First Reinoculation	After Second Reinoculation	
Hypervitamin rats	13	4	0	0	9
Control rats	13	5	0	0	8
Males	13	2	0	0	11
Females	13	7	0	0	6
Hypervitamin males	6	1	0	0	5
Control males	7	1	0	0	6
Hypervitamin females	7	3	0	0	4
Control females	6	4	0	0	2

TABLE 6.—*Results of Intragastric Instillation of the Virus*

Animals	Number of Animals	Paralyzed in 2 or More Extremities Within Usual Incubation Period			Resistant to 2 Three Way Reinoculations
		After Experimental Instillation	After First Reinoculation	After Second Reinoculation	
Hypervitamin rats	13	1	10	1	1
Control rats	15	0	13	0	2
Males	15	0	14	0	1
Females	13	1	9	1	2
Hypervitamin males	7	0	6	0	1
Control males	8	0	8	0	0
Hypervitamin females	6	1	4	1	0
Control females	7	0	5	0	2

gastrointestinal tract. Each cotton rat was subjected to a single intracolonic instillation of 1.0 cc. of a 10 per cent suspension of the virus administered by means of a rectal tube. Table 7 summarizes the results of this experiment.

EXPERIMENT 7.—This experiment was performed in order to determine whether the vitamin intake of the host might influence its response to the virus of poliomyelitis when the latter is injected into the peritoneal cavity. Each cotton rat was subjected to a single intraperitoneal inoculation with 1.0 cc. of a 10 per cent suspension of the virus. Table 8 summarizes the results of this experiment.

Part 3. Comparative Response of Rats on a Hypervitamin Diet and of Control Rats Subjected to Inoculations of the Virus Into Different Parts of the Respiratory Tract.

EXPERIMENT 8.—This experiment was performed in order to determine whether the vitamin intake of the host might influence its response to the virus of poliomyelitis when the latter is instilled into the external nares. Each cotton rat was subjected during the morning and again

TABLE 7.—*Results of Intracolonic Instillation of the Virus*

Animals	Number of Animals	Paralyzed in 2 or More Extremities Within Usual Incubation Period			Resistant to 2 Three Way Reinoculations
		After Experimental Instillation	After First Reinoculation	After Second Reinoculation	
Hypervitamin rats	14	0	12	1	1
Control rats	15	1	11	1	2
Males	13	0	10	1	2
Females	16	1	13	1	1
Hypervitamin males	6	0	5	0	1
Control males	7	0	5	1	1
Hypervitamin females	8	0	7	1	0
Control females	8	1	6	0	1

TABLE 8.—*Results of Intraperitoneal Inoculation with the Virus*

Animals	Number of Animals	Paralyzed in 2 or More Extremities Within Usual Incubation Period			Resistant to 2 Three Way Reinoculations
		After Experimental Inoculation	After First Reinoculation	After Second Reinoculation	
Hypervitamin rats	13	0	2	0	11
Control rats	12	0	2	0	10
Males	12	0	3	0	9
Females	13	0	1	0	12
Hypervitamin males	6	0	2	0	4
Control males	6	0	1	0	5
Hypervitamin females	7	0	0	0	7
Control females	6	0	1	0	5

during the evening to an intranasal instillation of the virus. On each of these two occasions 0.05 cc. of a 10 per cent suspension of the virus was dropped into each nostril. Table 9 summarizes the results of this experiment.

EXPERIMENT 9.—This experiment was performed in order to determine whether the vitamin intake of the host might influence its response to the virus of poliomyelitis when the latter is instilled into the lower part of the respiratory tract. Each cotton rat was subjected to a single instillation of 0.1 cc. of a 10 per cent suspension of the virus into the lower part of the trachea administered by means of a tracheal tube. Table 10 summarizes the results of this experiment.

Part 4. Comparative Response of Rats on a Hypervitamin Diet and of Control Rats Subjected to Inoculations with the Virus Through Certain Unusual Portals.

EXPERIMENT 10.—This experiment was performed in order to determine whether the vitamin intake of the host might influence its response to the virus of poliomyelitis when the latter is injected beneath the skin. Each cotton rat was subjected to a single subcutaneous inoculation with

TABLE 9.—*Results of Intranasal Instillation of the Virus*

Animals	Number of Animals	Paralyzed in 2 or More Extremities Within Usual Incubation Period			Resistant to 2 Three Way Reinoculations
		After Experimental Instillation	After First Reinoculation	After Second Reinoculation	
Hypervitamin rats	13	0	11	1	1
Control rats	12	0	12	0	0
Males	12	0	11	0	1
Females	13	0	12	1	0
Hypervitamin males	6	0	5	0	1
Control males	6	0	6	0	0
Hypervitamin females	7	0	6	1	0
Control females	6	0	6	0	0

TABLE 10.—*Results of Instillation of the Virus Into the Lower Part of Respiratory Tract*

Animals	Number of Animals	Paralyzed in 2 or More Extremities Within Usual Incubation Period			Resistant to 2 Three Way Reinoculations
		After Experimental Instillation	After First Reinoculation	After Second Reinoculation	
Hypervitamin rats	12	0	10	0	2
Control rats	13	0	11	0	2
Males	13	0	11	0	2
Females	12	0	10	0	2
Hypervitamin males	6	0	5	0	1
Control males	7	0	6	0	1
Hypervitamin females	6	0	5	0	1
Control females	6	0	5	0	1

1.0 cc. of a 10 per cent suspension of the virus. In each case, injections were made into the superficial fascia of the back. Table 11 summarizes the results of this experiment.

EXPERIMENT 11.—This experiment was performed in order to determine whether the vitamin intake of the host might influence its response to the virus of poliomyelitis when the latter is injected into the blood stream. Each cotton rat was subjected to a single intracardiac inoculation with 0.5 cc. of a 10 per cent suspension of the virus. Table 12 summarizes the results of this experiment.

EXPERIMENT 12.—This experiment was performed in order to determine whether the vitamin intake of the host might influence its response to the virus of poliomyelitis when it is subjected to the latter by means of contact with a diseased rat. Each cotton rat was permitted to live in the same cage with another cotton rat which had been subjected to a three way inoculation with a 10 per cent suspension of the virus. The experimental cotton rat remained in intimate contact with the inoculated

TABLE 11.—*Results of Subcutaneous Inoculation with the Virus*

Animals	Number of Animals	Paralyzed in 2 or More Extremities Within Usual Incubation Period			Resistant to 2 Three Way Reinoculations
		After Experimental Inoculation	After First Reinoculation	After Second Reinoculation	
Hypervitamin rats	12	0	0	0	12
Control rats	15	1	0	0	14
Males	13	0	0	0	13
Females	14	1	0	0	13
Hypervitamin males	6	0	0	0	6
Control males	7	0	0	0	7
Hypervitamin females	6	0	0	0	6
Control females	8	1	0	0	7

TABLE 12.—*Results of Inoculation of the Virus Into the Blood Stream*

Animals	Number of Animals	Paralyzed in 2 or More Extremities Within Usual Incubation Period			Resistant to 2 Three Way Reinoculations
		After Experimental Inoculation	After First Reinoculation	After Second Reinoculation	
Hypervitamin rats	13	3	1	0	9
Control rats	14	2	0	0	12
Males	13	2	1	0	10
Females	14	3	0	0	11
Hypervitamin males	6	1	1	0	4
Control males	7	1	0	0	6
Hypervitamin females	7	2	0	0	5
Control females	7	1	0	0	6

animal until the latter became completely paralyzed. Table 13 summarizes the results of this experiment.

COMMENT

None of these experiments yielded results which would indicate that susceptibility to the virus of poliomyelitis is related to the vitamin or to the caloric intake of the host.

In each of 5 experiments ("intratonsillar," intragastric, intracolonic, subcutaneous and intracardiac) 1 or more of the experimental animals contracted anterior poliomyelitis without being subjected to an intracere-

bral inoculation with the virus. In previous investigations [2] we have shown that the cotton rat may occasionally contract the paralytic form of the disease even though the virus is administered by these extracerebral routes only. As in our previous experience, the cotton rat is especially susceptible to the paralytic form of the disease when the virus is administered by the "intratonsillar" or by the intracardiac route.

Of the 17 cotton rats in which the paralytic form of the disease developed after the virus was administered by extracerebral routes only,

TABLE 13.—*Comparative Results of Contact Between an Inoculated and an Uninoculated Animal*

Animals	Number of Animals	Paralyzed in 2 or More Extremities Within Usual Incubation Period			Resistant to 2 Three Way Reinoculations
		After Experimental Contact	After First Reinoculation	After Second Reinoculation	
Hypervitamin rats	12	0	12	0	0
Control rats	13	0	12	0	1
Males	13	0	13	0	0
Females	12	0	11	0	1
Hypervitamin males	6	0	6	0	0
Control males	7	0	7	0	0
Hypervitamin females	6	0	6	0	0
Control females	6	0	5	0	1

13 were females. This unusual susceptibility of the female to the paralytic form of the disease was especially evident in experiment 4, in which the virus was administered by "intratonsillar" injection. In this experiment, 3 out of 7 females on the hypervitamin diet and 4 out of 6 control females became paralyzed as compared to 1 out of 6 males on the hypervitamin diet and 1 out of 7 control males. I am unable to account for the increased susceptibility exhibited by the females.

The findings reported in this communication agree with our previous experience [2] that the majority of cotton rats build up complete resistance to intracerebral inoculations if such inoculations are preceded by "intratonsillar," intracardiac, intraperitoneal or subcutaneous injections of the virus. A smaller percentage of cotton rats acquire this resistance after intratracheal, intranasal, intragastric or intracolonic instillations of relatively large quantities of the virus, after contact with a cotton rat succumbing to the disease or after devouring a brain stem and spinal cord which have been removed from a rat infected with the virus of

2. Weaver, H. M.: (*a*) Effect of Rachitogenic Diet, Partial Inanition, and Sex on the Resistance of Cotton Rats to Virus of Poliomyelitis, J. Pediat. **24**:88-105, 1944; (*b*) Resistance of Cotton Rats to Virus of Poliomyelitis as Affected by Intake of Vitamin B Complex, Partial Inanition and Sex, Am. J. Dis. Child. **69**:26-32 (Jan.) 1945; (*c*) Resistance of Cotton Rats to Virus of Poliomyelitis, as Affected by Intake of Vitamin A, Partial Inanition and Sex, J. Pediat. **28**:14-23 (Jan.) 1946.

poliomyelitis. These experiments offered no evidence to indicate that the capacity of cotton rats to develop such resistance was related to vitamin intake or to sex.

SUMMARY AND CONCLUSIONS

Twelve experiments were performed which were designed to test the effects of vitamin and caloric intake and of sex on the susceptibility and on certain immunologic responses of cotton rats to the virus of poliomyelitis. The diet which was fed to the experimental animals contained ten times the quantity of purified vitamins in that which was fed to the controls.

Suspensions of the Armstrong-Lansing strain of the virus of poliomyelitis were injected or instilled in varying quantities into the cerebrum, stomach, colon, peritoneal cavity, external nares, trachea and blood stream, beneath the skin of the back and beneath the pharyngeal mucosa. In addition, the animals of one experimental group were allowed to remain in intimate contact with cotton rats which were succumbing to the effects of intracerebral inoculations with the virus. Finally, each cotton rat of still another experimental group was fed the brain stem and spinal cord freshly removed from a cotton rat paralyzed with poliomyelitis.

Each of the cotton rats in which paralysis failed to develop after an experimental inoculation with the virus was subjected to three way reinoculations with the virus at intervals of twenty-five days.

The results of this work yield no evidence to indicate that vitamin or caloric intake significantly affects the susceptibility of cotton rats to the Armstrong-Lansing strain of the virus of poliomyelitis. Furthermore, no evidence was found that the resistance of cotton rats to three way reinoculations with the virus, administered subsequently to any of the experimental inoculations, is influenced by the vitamin or caloric intake or by sex.

Attention was called to the apparent increased susceptibility of the female to the paralytic form of the disease following inoculations with the virus by various extracerebral routes.

CELIAC SYNDROME

IV. Chemotherapy in Infections of the Respiratory Tract Associated with Cystic Fibrosis of the Pancreas; Observations with Penicillin and Drugs of the Sulfonamide Group, with Special Reference to Penicillin Aerosol

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THE clinical recognition of congenital pancreatic deficiency has become more frequent in recent years with the clearer delineation of the clinical features of the disease and the possibility of confirming the diagnosis by assay of the duodenal juice for pancreatic enzymes.[1] The problems of therapy have become correspondingly pressing. Treatment directed toward the nutritional difficulty has been discussed in a previous paper.[2] Treatment of infection of the respiratory tract forms the subject of the present report. There is evidently a close relationship between the nutritional difficulty and the infection of the respiratory tract, since the latter has not appeared in those few patients who have received appropriate dietary therapy prior to the onset of a chronic cough.[2] It seems reasonable to believe that the failure of these children to absorb adequate amounts of vitamin A on a normal diet may contribute to their susceptibility to bronchitis. but other factors also are probably concerned. Dietary therapy begun after the onset of infection of the respiratory tract decreases the mortality and prolongs the life of many patients. Once the infection is well established, however, dietary therapy is only occasionally effective. Methods of direct attack on the infection itself should be sought. An investigation of the effectiveness of the several chemotherapeutic agents which have become available in recent years is a logical approach to the problem.

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1. Andersen, D. H.: Pancreatic Enzymes in the Duodenal Juice in the Celiac Syndrome, Am. J. Dis. Child. **63**:643-658 (April) 1942.

2. Andersen, D. H.: Celiac Syndrome: III. Dietary Therapy for Congenital Pancreatic Deficiency, Am. J. Dis. Child. **70**:100-113 (Aug.) 1945.

COURSE OF INFECTION OF THE RESPIRATORY TRACT IN THE ABSENCE OF CHEMOTHERAPY

The general pattern of the course of infection of the respiratory tract is strikingly uniform. The chief differences are the age at which the infection appears, the length of the phases and the length of survival. The cough is not present at birth and may make its appearance at any time after the first week, most commonly between the second and sixth month. It often follows a mild coryza and appears as an infrequent dry cough not accompanied with hyperthermia. After a few days or weeks this merges into a paroxysmal cough suggestive of the cough of pertussis without a whoop. This is usually accompanied with a decrease or cessation of gain in weight, but usually not with fever. Roengenograms of the chest taken during the earlier part of the period may show no abnormalities, but later they show increased bronchovascular markings bilaterally and a diagnosis of bronchopneumonia is usually made. Abnormalities observed on physical examination of the chest are: increase in the anterior-posterior diameter of the thorax, increase in rate of respirations, hyperresonance and coarse moist rales and sometimes rhonchi best heard in the interscapular region. The temperature is commonly normal but may show low spikes; these may occur in the morning or in the afternoon. High spikes for one or two days, not accompanied with changes in the clinical appearance or the physical condition, may occur and are unexplained. The initial clinical diagnosis is usually bronchopneumonia, pertussis or lipid pneumonia. After an interval of several weeks or months during which the symptoms and signs show little change, the respiratory difficulty increases in severity. Respirations become more rapid, and there are pronounced subcostal, intercostal and suprasternal retractions. Cyanosis appears during bouts of coughing and presently becomes continuous. The fingers and toes become clubbed. The cough is productive of thick mucopurulent sputum. Spasms of coughing may be prolonged and exhausting; they may be stimulated by change of position or by eating, and they often result in vomiting. Roentgenograms taken during this phase of the disease show many "snowflake" areas of increased density, which resemble those of disseminated tuberculosis, in addition to the increased hilar markings previously evident. During this terminal phase there may be anorexia, or the appetite may remain excellent. It is not unusual for an infant who cannot be removed from an oxygen tent without becoming cyanotic to consume 150 calories per kilogram with relish. The temperature is unpredictable and may still remain normal or show low spikes or a few days before death it may become high. A few marasmic infants have

hypothermia. More deaths result from asphyxia than from toxemia, and death may occur suddenly.

In a few of the cases with early onset the initial cough disappears gradually after some weeks. The infant undergoes prolonged periods of coughing after each subsequent infection of the respiratory tract. The course then follows a pattern similar to that of the patients with a later onset.

In the patients with a late onset, those in whom the cough is first noted after the sixth month, the infant has a series of prolonged "colds" complicated by bronchitis or bronchopneumonia during the first two or three winters. Presently there comes a winter during which the cough is chronic and becomes progressively severe and more productive. During this period the temperature is normal or shows temporary mild rises. The weight becomes static and may decrease. Cyanosis appears, at first only during bouts of coughing, and the fingers become clubbed. The respiratory difficulty may remain apparently static for many months and then become severer over a period of a few weeks or months, terminating in the same manner as in the cases with earlier onset.

There are occasional children who reach the age of 5 years or more without therapy based on a correct diagnosis, in whom cyanosis has not developed. They do, however, have a chronic cough and may be admitted to the hospital with the diagnosis of bronchiectasis, chronic sinusitis or chronic otitis media. Six such patients have been encountered, 3 of them without retardation of growth. These children had all received a diet restricted in fats, either because of clinical intolerance to fat in the form of diarrhea following ingestion of fat or because the association of an enlarged abdomen and large foul stools led to a diagnosis of celiac disease.

The interval between the onset of the cough and the appearance of cyanosis is therefore variable. It is shorter for patients with an onset of cough in the first few months of life than for those in whom respiratory symptoms first develop at a later date. The interval between the time when cyanosis is first noted and death is less than a month in the majority of cases, though occasionally it is much longer, especially in cases in which there is a late onset. The development of severe respiratory embarrassment is usually gradual, but it may be so sudden that the day of transition can be named, and when this is the case death follows within one to three weeks.

Few laboratory determinations have proved helpful in evaluating the course of the infection. Cultures of materials from the nose and throat yield hemolytic Staphylococcus aureus often accompanied with other pathogenic organisms. During acute infections of the upper respiratory tract a streptococcus or pneumococcus is often temporarily

present. Roentgenograms of the chest show increased bronchovascular markings at all phases of the infection of the respiratory tract, except during the first weeks following the initial appearance of the cough. Occasionally there are small shadows interpreted as localized areas of atelectasis which persist over months and years. The "snowflake" shadows of the terminal phase have been mentioned. Our experience with bronchograms taken after instillation of iodized poppyseed oil is too limited for analysis; mild tubular dilatation of the bronchi, especially of the lower lobes, has been found on occasion.

The leukocyte count is of value in estimating the effects of therapy and, to some extent, the prognosis. When it remains high in spite of clinical improvement, a subsequent exacerbation of clinical symptoms may be expected. A persistently normal leukocyte count in the presence of a mild chronic cough may be followed by gradual disappearance of the cough with dietary therapy as the only treatment.

The sedimentation rate is usually within normal limits except when cultures of material from the nose and throat yield other pathogenic organisms in addition to the hemolytic Staph. aureus.

POSTMORTEM OBSERVATIONS OF THE RESPIRATORY TRACT

The lesions of the respiratory tract are in part chronic and in part acute. The chronic lesion is bronchitis involving the secondary and tertiary bronchi within the substance of the lung and to a lesser degree the primary bronchi and trachea. The intrapulmonary bronchi are thickened with fibrous tissue and infiltrated with many lymphocytes and plasma cells. They may show a tubular dilatation. In the primary bronchi and in the trachea also, there is an infiltration of lymphocytes beneath the epithelium, but this is often mild and the mucous glands are little involved. The reaction decreases with the distance from the lung and is mild in the upper part of the trachea. These chronic changes account for the thickened bronchovascular markings of the roentgenograms.

Superimposed on this basic process, there is an acute suppurative bronchitis, resulting in more or less occlusion of the bronchial lumens with thick mucopurulent material; the bronchial tree and the trachea may appear completely filled with this material up to the larynx. Section of the fresh lung gives a striking picture, with pus welling from every bronchus to form whitish mounds against a fairly homogeneous pale pink parenchyma. The obstruction of the air passages clearly explains the difficulty in respiration and the death from asphyxia. Careful observation of the intrapulmonary bronchi demonstrates that those large enough to be provided with cartilage usually show both a chronic and an acute process. Those next smaller may be similar, often with the acute process predominating and with an intact bronchial

epithelium. The smallest bronchioles may show acute changes only or they may be normal except for dilatation. The changes are more chronic and more extreme in the larger and medium-sized intrapulmonary bronchi than they are in the bronchioles and primary bronchi.

Changes in the alveoli are of three types. The majority of the alveoli are emphysematous and free from exudate. There are lobules or groups of lobules near the ends of the middle-sized bronchi which present the picture of acute lobular pneumonia or of bronchiogenic abscesses. Along the thinner margins of the lung, especially on the

TABLE 1.—*Postmortem Cultures—Cystic Fibrosis of the Pancreas January 1939 to June 1945*

Case No.[23]	Age, Mo.	Lung		Other Organs
		Predominating Organism	Also Present	
S2	4	Hemolytic Staph. aureus	A few pneumococci, type 14	Trachea: Staph. only
S3	2½	Pneumococcus, type 25	Many hemolytic Staph. aureus; a few nonhemolytic Staph. albus	
S8	15	Hemolytic Staph. aureus (m+c+)	Moderate number Hemophilus influenzae (not B)	
S10	4	Hemolytic Staph. aureus (m+c+)		
S15	4	Hemolytic Staph. aureus (m+c+)	Hemolytic Str., a few	
S16	15	Hemolytic Staph. aureus (m+c+)	Hemolytic Str.	Bronchus: Staph. and Str.
S18	11	Hemolytic Staph. aureus (m+c+)		
S19	15	Hemolytic Staph. aureus (m+c+)		
S20	2	Hemolytic Staph. aureus (m+c+)	.....	Ear: Staph. aureus (m+c+); a few B. coli
S23	12	No culture. Microscopic examination: clumps of gram-positive cocci, morphologically staphylococci		
S25	32	Hemolytic Staph. aureus (m+c+)	B. pyocyaneus	
S30	9	Hemolytic Staph. aureus (m+c—)	A few Str. viridans, B. coli	
S33	1	No growth		
S37 (12)	40	Hemolytic Staph. aureus (m+c+)	.....	Trachea: Staph. aureus (m+c+); a few diphtheroids

M+c+ = mannitol fermenting and coagulase positive.

anteromedial margins and the lateral margins of the lower lobes, there are small triangular areas of atelectasis. On microscopic examination these ordinarily appear of recent origin, but occasionally they may be organized and of long standing.

Postmortem cultures of the lung have been made in 13 cases (table 1). No growth was obtained from the lung of an infant dying at 4 weeks of severe diarrhea; this case was the only one of the series in which the characteristic pulmonary changes were absent. In the remaining 12 cases hemolytic Staph. aureus was present and was the predominant organism in all except 1. It was the sole organism

obtained in 4 cases, and in the remainder there were various associated bacteria. These cases are in addition to those reported in 1938 [3] and tend to confirm the earlier conclusion that Staphylococcus is the usual bacterial agent in the pulmonary infection associated with congenital pancreatic deficiency.

RESULTS OF CHEMOTHERAPY WITH THE SULFONAMIDE DRUGS

These clinical studies of pancreatic deficiency were begun in 1939, after the first of the drugs of the sulfonamide group became available. The diagnosis of pancreatic deficiency was based either on the presence of excess fecal fat and the absence of trypsin from the duodenal juice or on postmortem examination. The majority of the patients in the present series have received some form of chemotherapy. During these years sulfanilamide, sulfapyridine, sulfathiazole and sulfadiazine have one by one become available and have been used, sometimes successively for the same patient. The record is not clear as to their relative effective-

TABLE 2.—*Clinical Results of Therapy with Drugs of the Sulfonamide Group*

Beginning of Therapy	Results		
	Poor	Good	Total
After onset of cyanosis	18	1 (?)	19
Before cyanosis, during chronic cough; for treatment of intercurrent infection	1	8	9
During chronic cough; prophylaxis of sequelae of intercurrent infections	0	8	8

ness in various circumstances in this disease. In the present summary no distinction is made between them. In the earlier cases sulfathiazole was usually used, and during the past few years sulfadiazine has been used almost exclusively. Penicillin first became available to us in limited quantities in the spring of 1943, and since then it has been used in conjunction with drugs of the sulfonamide group. Observations on the effects of these drugs alone may be said to have terminated in the summer of 1944, when supplies of penicillin became adequate.

The effectiveness of the sulfonamide drugs in the treatment of infections of the respiratory tract associated with congenital pancreatic deficiency depends on the phase of the infection (table 2). They are without apparent effect after the appearance of severe respiratory distress accompanied with cyanosis. In spite of this, they were used hopefully in each case seen before the era of penicillin, since other therapy was equally ineffective. During the stage of chronic cough without

3. Andersen, D. H.: Cystic Fibrosis of the Pancreas and Its Relation to Celiac Disease: A Clinical and Pathologic Study, Am. J. Dis. Child. **56**:344-399 (Aug.) 1938.

cyanosis a fresh cold or infection of the respiratory tract due to pneumococci or streptococci is usually followed by an exacerbation of the cough lasting many weeks. Repetition of this process at intervals of a month or two has a cumulative effect. These acute infections often respond promptly to the administration of sulfadiazine, and sequelae are often averted. Absence of the sequelae of coryza and pharyngitis over prolonged periods also has a cumulative effect, leading to the gradual decrease and the ultimate disappearance of the cough; this statement should be qualified by the condition that the dietary therapy is concurrent and appropriate. The combination of dietary therapy and the control of fresh infections with sulfadiazine accounts for the survival of the majority of the living patients of our series and of all those who have survived the prepenicillin period. Even now, when penicillin is available, a prompter control of intercurrent infections due to streptococci or pneumococci is obtained with sulfadiazine.

The prophylactic use of sulfadiazine has been especially effective. During the winter of 1944-1945, small doses of sulfadiazine, 0.25 Gm. twice a day, were given as prophylaxis to 8 patients between the ages of 18 months and 7 years. Six of these children had previously received one or more courses of penicillin aerosol. These patients all had had several colds each winter in former years, usually followed by a nasal discharge and an increase in cough for some weeks. During the winter of 1944-1945 they had two or three colds each, with 1 exception, lasting no more than three days and terminating without an increase in the cough. One boy of 7 (case 26) had three colds during the winter of 1943-1944 which were so prolonged as to merge into one another. During the next winter while taking prophylactic doses of sulfadiazine, he had two episodes of coryza lasting a few days each and a third, which was followed by bronchitis. After three weeks of coughing he received therapy with penicillin aerosol with a prompt relief of symptoms. This is the only example of partial failure of prophylaxis with sulfadiazine.

Experience with the prophylactic use of sulfadiazine has not been sufficient to form the basis of a definitive pronouncement as to the best method of use and the degree of benefit to be expected. The present tentative policy is to give a daily dose of 0.5 Gm. to all patients who have a cough and to those who have received penicillin for the treatment of severer symptoms within recent months, whether or not they cough at present. After tolerance to the drug has been ascertained by several leukocyte counts at biweekly intervals, these counts are made monthly. Patients who have been free from cough for many months do not receive the drug regularly, but they are provided with a small supply and advised that on the first appearance of a fresh infection the first dose should be taken at once and the physician should be notified.

In summary, drugs of the sulfonamide group are of great value in the prophylaxis and treatment of a recently acquired infection of the upper respiratory tract in patients with congenital pancreatic deficiency. They have little effect on chronic bronchitis and usually have none whatever after the appearance of cyanosis marks the terminal phase of the disease.

RESULTS OF THERAPY WITH INTRAMUSCULAR ADMINISTRATION OF PENICILLIN

In 5 cases of cystic fibrosis of the pancreas complicated by staphylococcic bronchopneumonia, the patients have been treated by intramuscular injections of penicillin. These cases may be divided into two groups. Group A includes cases 1, 2, and 3, in which the patients were treated in 1943 with small amounts of penicillin given daily over periods of several weeks. This restricted schedule of therapy was due to the limited supply of penicillin available at that time. Group B consists of cases 4 and 5. In the latter 2 the patients were treated during 1944 when the supply of penicillin was plentiful, and they therefore received larger amounts of the drug.

In the 3 cases of group A the patients responded satisfactorily to the first course of penicillin therapy. Especially dramatic improvement was noted in case 1, that of a 3 month old baby, with scattered patches of pulmonary consolidation and pulmonary abscesses, which disappeared so completely after therapy that no roentgenologic evidence of a pathologic pulmonary condition could be found. In this, as in other cases, the improvement continued for some weeks after the treatment had been discontinued. No penicillin could be obtained on the recurrence of the symptoms five months later, and the patient died of an overwhelming staphylococcic infection of the lungs after an illness of six weeks.

In case 2 the staphylococci isolated from material obtained by puncture of the lung before the administration of the drug were shown to be sensitive to penicillin in vitro. A culture obtained by puncture of the lung some time after completion of the first course of therapy, on the other hand, yielded an organism which was completely resistant. On recurrence of the bronchopneumonia penicillin therapy was again resumed, but the results were unsatisfactory and the patient eventually died.

In case 3 there was a response to chemotherapy but it was impossible to obtain further supplies of penicillin for continuance of the second course, and after five months of hospitalization the child died.

In case 4 of group B the patient never responded to penicillin therapy and died after a hospital stay of three months. This patient received large amounts of penicillin by intramuscular injection for long

periods (table 3). An attempt was made to give penicillin by inhalation, but because of mechanical difficulties an insignificant amount of drug was given by this method. The strain of staphylococcus isolated from the lungs at autopsy was found to survive a concentration of 250 Oxford units of penicillin per cubic centimeter. Unfortunately, no titration of sensitivity to penicillin had been made prior to the therapy, but the poor response to the drug from the beginning leads to the suspicion that the infecting organism belonged to the group of staphylococci naturally resistant to penicillin.

Case 5 is the only one in the aforementioned two groups in which the ultimate result of penicillin therapy was satisfactory. As can be seen from the detailed history of this case, the patient responded well to penicillin given intramuscularly and introduced directly into a pulmonary abscess. After a second infection another course of intramuscular therapy was given in December 1944. Following this, the baby remained well for about five months and during this time regained much of the ground lost in her growth and development.

Although still in good physical condition she was readmitted in May 1945 because of recurrence of the cough. She again responded to penicillin therapy. An acute pharyngitis in August responded promptly to sulfadiazine, and she is now normal as to nutrition and activity and without a cough, at the age of 21 months (September 1945).

Several facts stand out from this brief survey of our experiences in the treatment of the staphylococcic pneumonia of patients with congenital pancreatic deficiency by the intramuscular administration of penicillin. First, evaluation of the results of therapy is difficult because of the small number of cases and the variability in the sensitivity of the organisms to penicillin. It seems reasonable to assume that the failure of the drug in case 2 was due to the resistance to penicillin which the organism had acquired during treatment, and in case 4 the failure of therapy was the consequence of the resistance of the organism to penicillin from the beginning. In the cases of group A the limited supplies of penicillin and the lack of experience on our part contributed to a schedule of therapy in which the daily doses were clearly inadequate. It is our present belief that larger doses of penicillin over shorter periods would have produced more satisfactory results. Taking these acknowledged flaws in the mode of therapy into consideration, one may conclude that the staphylococcic pneumonia of patients with pancreatic deficiency may respond to the intramuscular administration of penicillin. Four of the 5 patients responded in varying degrees. One patient (case 5), who was the only one to receive adequate therapy, rallied to the treatment with gratifying and, so far, enduring results.

TABLE 3.—*Results of Penicillin Therapy on the Suppurative Bronchopneumonia of Patients with Cystic Fibrosis of the Pancreas*

Pulmonary Infection					Penicillin Therapy			Dosage			
Case, No.	Sex	Age on Admission	Age at Onset	Type	Course, No.	Dates of Therapy	No. of Days	Intramuscular, U/24 Hr.	Inhalation, U/24 Hr.	Total Units per Course	Results
Group I. Patients Treated by Intramuscular Administration of Penicillin											
1 (S 18) J. A.	M	7 wk.	4 mo.	Multiple pulmonary abscesses (April 1943)	1	4/20/43 to 5/22/43	33	20,000	.....	624,000	Complete cure of pulmonary abscesses, April, 1943
				Diffuse chronic bronchopneumonia (October 1943)	..	.....	..	.....	.....	.....	Death on recurrence, (October 1943) when penicillin was not available
2 (S 19) M. G.	F	9 mo.	3 mo.	Chronic disseminated bronchopneumonia	1	6/12/43 to 6/26/43	14	20,000	.....	235,000	Pronounced improvement after first course
				Pulmonary abscesses	2	8/30/43 to 9/19/43	22	40,000 later 20,000	.....	510.000	Only slight transient improvement after second course (Staph. aureus became resistant to penicillin); died, 11/22/43
						Total.....	36	.....	.....	745,000	
3 (S 25) J. M.	F	2 yr., 2 mo.	2 yr., 2 mo.	Diffuse chronic bronchopneumonia; bronchiectasis	1	12/19/43 to 1/2/44	14	15,000	.....	190,000	Pronounced improvement after first course
				Pulmonary abscesses	2	2/20/44 to 4/11/44	51	15,000 to 20,000	.....	850,000	Some response after second course; death when penicillin was no longer available
						Total.....	65	.....	.....	1,040,000	
4 (S 30) N. M.	M	8 mo.	Birth	Chronic bronchopneumonia	1	8/7/44 to 8/25/44	17	32,000	.....	464,000	No response to treatment; died, 10/19/44; (Staph. aureus obtained from lungs at autopsy, resistant to penicillin)
				Atelectasis	2	9/ 1/44 to 9/12/44	12	32,000	.....	430,000	
					3	9/15/44 to 9/29/44	15	32,000	.....	580,000	
					4	10/11/44 to 10/18/44	7	50,000	.....	250,000	
						Total.....	51	.....	.....	1,724,000	
5 (S 36) J. E.	F	1 yr.	7 mo.	Bilateral chronic bronchopneumonia	1	1/26/45 to 1/30/45	5	160,000	.....	640,000	Pronounced and continued improvement; lungs normal on physical examination
					2	2/ 5/45 to 2/ 8/45	4	160,000	.....	560,000	
					3	2/27/45 to 3/ 4/45	6	160,000	.....	820,000	
						Total.....	15	.....	.....	2,020,000	

Group II. Patients Treated with Penicillin Aerosol or with the Administration of Penicillin by the Intramuscular and Inhalational Routes Combined

6 (S 24) R. H.	M	16 mo.	2 mo.	Bilateral chronic bronchopneumonia Consolidated middle lobe, right lung Bronchiectasis	1	7/26/44 to 8/ 3/44	9	.....	32,000	272,000	Slight transient improvement
					2	8/14/44 to 8/21/44	8	.....	56,000	424,000	
							4	32,000	.....	96,000	
					3	8/26/44 to 8/29/44	9	.....	32,000	264,000	
					4	9/ 1/44 to 9/ 9/44	11	.....	100,000	1,000,000	
					5	10/27/44 to 11/ 6/44	7	.....	280,000	1,560,000	
					6	2/20/45 to 2/26/45	5	160,000	200,000	1,800,000	
					7	3/ 5/45 to 3/ 9/45	4	160,000	100,000	1,040,000	
					8	3/16/45 to 3/19/45	10	200,000	140,000	3,445,000	
					9	4/27/45 to 5/ 6/45					
						Total.....	66	.....	.....	9,901,000	
7 (S 29) M. N.	F	4 yr., 3 mo.	3 yr., 8 mo.	Extensive bilateral bronchopneumonia Bronchiectasis (?)	1	7/27/44 to 8/ 8/44	13	.....	32,000	368,000	Pronounced, immediate and continued improvement
					2	8/15/44 to 8/22/44	8	.....	32,000	240,000	
					3	9/ 1/44 to 9/12/44	12	.....	32,000	352,000	Loss of cough and clubbing; lungs normal on physical examination
					4	11/ 6/44 to 11/ 7/44	2	.....	100,000	210,000	
					5	11/ 9/44 to 11/10/44	2	45,000	180,000	450,000	
					6	12/ 2/44 to 12/ 5/44	4	.....	180,000	640,000	
					7	2/15/45 to 2/21/45	7	160,000	100,000	1,560,000	
					8	2/28/45 to 3/ 6/45	7	160,000	120,000	1,580,000	
						Total.....	55	.....	.....	5,400,000	
8 (S 32) S. P.	F	15 mo.	3 mo.	Chronic bronchitis	1	9/26/44 to 10/ 4/44	9	.....	40,000	314,000	Pronounced and continued improvement
					2	10/14/44 to 10/25/44	12	.....	50,000	525,000	Disappearance of all pulmonary changes in the roentgenograms
						Total.....	21	.....	.....	839,000	
9 (S 6) J. R.	F	5 yr., 8 mo.	.....	Chronic bilateral bronchopneumonia	1	10/ 4/44 to 10/14/44	11	.....	50,000	500,000	Pronounced and continued improvement (clinically a complete return to normal)
					2	10/21/44 to 10/31/44	11	.....	50,000	500,000	
						Total.....	22	.....	.....	1,000,000	
10 (S 34) J. R.	F	5 yr., 9 mo.	8 mo.(?)	Mild chronic bilateral bronchopneumonia	1	11/16/44 to 11/19/44	4	.....	80,000	300,000	Only slight improvement
					2	1/ 5/45 to 1/10/45					
					3	1/19/45 to 1/24/45	6	.....	100,000	492,000	
					4	2/21/45 to 2/26/45	6	.....	100,000	500,000	
							6	.....	200,000	1,050,000	
						Total.....	22	.....	.....	2,432,000	

TABLE 3.—*Results of Penicillin Therapy on the Suppurative Bronchopneumonia of Patients with Cystic Fibrosis of the Pancreas—Continued*

Pulmonary Infection					Penicillin Therapy			Dosage			
Case, No.	Sex	Age on Admission	Age at Onset	Type	Course, No.	Dates of Therapy	No. of Days	Intramuscular, U/24 Hr.	Inhalation, U/24 Hr.	Total Units per Course	Results
11 (S 27) M. G.	F	2 yr., 9 mo.	6 mo.	Extensive bilateral bronchopneumonia Bronchiectasis (?)	1	11/17/44 to 11/22/44	6	.....	65,000	375,000	Response to therapy while on penicillin but recurrence of infection soon after discontinued treatment; died January 1943
					2	11/28/44 to 12/ 2/44	5	.....	200,000	795,000	
					3	1/27/45 to 2/ 2/45	7	160,000	100,000	1,440,000	
					4	2/13/45 to 2/18/45	6	140,000	80,000	1,160,000	
					5	4/ 5/45 to 4/20/45	16	.....	175,000	2,775,000	
					6	4/25/45 to 5/ 6/45	12	200,000	140,000	3,480,000	
						Total.....	52	.....	.....	10.025,000	
12 (S 37) E. D.	F	2 yr., 9 mo.	2 yr., 6 mo.	Severe chronic bilateral bronchopneumonia	1	12/15/44 to 12/19/44	5	.....	100,000	480,000	Improvement only after first courses of treatment; recurrence; died July 1945
					2	12/27/44 to 12/31/44	5	.....	160,000	660,000	
					3	1/18/45 to 1/24/45	7	.....	160,000	950,000	
					4	2/ 7/45 to 2/12/45	6	180,000	140,000	1,640,000	
					5	3/ 1/45 to 3/ 8/45	7	.....	160,000	980,000	
					6	3/16/45 to 3/21/45	6	.....	160,000	820,000	
					7	4/21/45 to 5/18/45	29	300,000 later 140,000	140,000	8,155,000	
					8	5/27/45 to 6/20/45	25	.....	140,000	3,360,000	
					9	7/17/45 to 7/26/45	8	210,000	210,000	3,280,000	
						Total.....	98	.....	.....	20,325,000	
13 (S 41) G. W.	M	3 yr., 9 mo.	3 yr., 1 mo.	Severe disseminated bilateral bronchopneumonia	1	3/ 9/45 to 3/14/45	6	.....	160,000	840,000	Pronounced and continued improvement
					2	4/ 5/45 to 4/15/45	11	.....	165,000	1,870,000	
					3	5/18/45 to 5/28/45	11	.....	140,000	1,540,000	
						Total.....	28	.....	.....	4,250,000	
14 (S 44) P. D.	F	4 yr., 1 mo.	2 yr.	Extensive bilateral chronic bronchopneumonia	1	4/23/45 to 5/ 4/45	12	200,000	160,000	4,320,000	Pronounced and continued improvement
					2	5/16/45 to 5/25/45	10	.....	140,000	1,200,000	
						Total.....	22	.....	.....	5,520,000	
15 (S 43) A. G.	M	6 mo.	1 mo.	Extensive bilateral chronic bronchopneumonia Atelectasis (?)	1	4/ 3/45 to 4/27/45	25	160,000	100,000	4,480,000	Mild transitory improvement; died
					2	5/10/45 to 6/15/45	37	230,000	.....	8,620,000	
						Total.....	62	.....	.....	13,100,000	

ADMINISTRATION OF PENICILLIN BY INHALATION (PENICILLIN AEROSOL)

History and Rationale of Penicillin Aerosol Therapy.—It is apparent that the results of treatment of the staphylococcic bronchopneumonia of patients with congenital pancreatic deficiency were not entirely satisfactory. While the doses of penicillin were admittedly inadequate, it was also felt that results might have been better if a higher local concentration of the drug in the bronchial mucosa had been obtained. This hypothesis seemed reasonable because the infection is known to be localized primarily in the thickened and poorly vascularized walls of the chronically infected medium-sized and small bronchi. Possible methods of applying the chemotherapeutic agents directly to the bronchial mucosa were therefore considered. Penicillin was the drug of choice because it is active against Staph. aureus and also because it does not diffuse rapidly, thus making it possible to attain and maintain high local levels of the drug. Another factor to be considered is that products of cellular destruction, so abundantly present in the bronchi of these patients, do not inhibit the action of penicillin.

The direct instillation of a solution of penicillin into the bronchial tree was first attempted. This was not a new idea, for as far back as 1924 Moore [4] advocated bronchial lavage for disinfection of the bronchial tree. Kolmer in 1933 [5] carried out extensive experiments with animals on the effects of the intrabronchial injection of various chemical disinfectants. More recently Norris [6] reported on his experiences with intratracheal and intrabronchial instillation of solutions of sulfonamide compounds into patients with bronchiectasis. Since these instillations were done through a bronchoscope, frequent bronchoscopies were required. Another disadvantage of the procedure was the difficulty of distributing the material uniformly among the various diseased segments of the bronchial tree.[6]

Intratracheal instillation of penicillin was performed on only 1 of our patients (case 3). A tracheotomy was done in order to suction out the abundant thick tenacious purulent material which obstructed the respiratory passages. Intramuscular injection and intratracheal instillation of penicillin were given concurrently. Eight hundred Oxford units in 1 cc. of isotonic solution of sodium chloride was instilled into the tracheotomy tube at intervals of four hours over a period of twelve days,

4. Moore, W. F.: Bronchiectasis and Pulmonary Abscess, S. Clin. North America **4**:87-96 (Feb.) 1924.

5. Kolmer, J. A.: Bronchial Disinfection and Immunization: I. The Effects in Rabbits of Intrabronchial Injections of Various Chemical Disinfectants, Arch. Int. Med. **51**:346-366 (March) 1933.

6. Norris, C. M.: Sulfonamides in Bronchial Secretion: The Effect of Sulfonamides in Bronchiectasis, J. A. M. A. **123**:667-670 (Nov. 13) 1943.

after which 160 units in 1 cc. was given for a further eleven days. The procedure invariably provoked a paroxysm of coughing, which resulted in the immediate expulsion of the instilled material. This method of administration has not been attempted again.

Further advance was temporarily halted for want both of penicillin and of knowledge of a means of applying it directly to the bronchi. Both difficulties were solved for us in July 1944 by Dr. Alvan L. Barach, of the Presbyterian Hospital, who was at that time investigating the treatment of asthma and bronchiectasis in adults by inhalation of penicillin aerosol. Through his help we were able to obtain both the necessary apparatus and adequate supplies of the drug and to benefit by his experience.[7]

The administration of drugs by inhalation is not a new method of therapy. It has been chiefly used in the treatment of bronchial asthma. As long ago as 1919, Heubner[8] made a thorough investigation of the possibilities of inhalation therapy and pointed out the beneficial effects of nebulized solutions of epinephrine in patients with asthma. An important advance was made by Graeser and Rowe[9] with the introduction of a handbulb nebulizer that provided a fine suspension of epinephrine in air. Barach and others[10] found the inhalation of epinephrine and related compounds of value not only in asthma but also in pneumonia, pulmonary edema and irritant gas poisoning.

More recently sulfonamide compounds have been administered by the inhalation method. Castex and others[11] in Argentina were the first to report on this method of therapy, and its results in treating

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7. Barach, A. L.; Silberstein, F. H.; Oppenheimer, E. T.; Hunter, T., and Soroka, M.: Inhalation of Penicillin Aerosol in Patients with Bronchial Asthma, Chronic Bronchitis, Bronchiectasis and Lung Abscess: Preliminary Report, Ann. Int. Med. **22**:485-509 (April) 1945.

8. Heubner, W.: Ueber Inhalation zerstäubter Flüssigkeiten, Ztschr. f. d. ges. exper. Med. **10**:269-332, 1919.

9. Graeser, J. B., and Rowe, A. H.: Inhalation of Epinephrine for Relief of Asthmatic Symptoms, J. Allergy **6**:415-420 (July) 1935.

10. (*a*) Barach, A. L.: Physiologically Directed Therapy in Pneumonia, Ann. Int. Med. **17**:812-819 (Nov.) 1942; (*b*) Principles and Practices of Inhalation Therapy, Philadelphia, J. B. Lippincott Company, 1944. (*c*) Segal, M. S.: Inhalational Therapy in the Treatment of Serious Respiratory Disease, New England J. Med. **229**:235-241 (Aug. 5) 1943; (*d*) Medical Progress: Inhalation Therapy, ibid. **230**:456-465 (April 13); 485-493 (April 20) 1944.

11. Castex, M. R.: Capdehourat, E. L., and Lavarello, A.: Nuevo tratamiento de las supuraciones broncopulmonares: acción curativa de un preparado sulfamídico nebulizada, Rev. Asoc. med. argent. **55**:85-89 (Feb.) 1941; Técnica de las nebulizaciones y sus principales ventajas terapeuticas, Arch. argent. de enferm. d. ap. respir. y tuberc. **9**:15-28 (March-April) 1941; Nuevo tratamiento de las supuraciones broncopulmonaires, ibid. **9**:29-40 (March-April) 1941.

bronchopulmonary suppuration were satisfactory. Stacey [12] reported decided improvement in patients with bronchiectasis after inhalation of a nebulized solution of sulfathiazole. Barach [13] showed that the inhalation of Promin (sodium p,p'-diaminodiphenylsulfone) prevented the development of experimental pulmonary tuberculosis in guinea pigs.

A few words should be said regarding the behavior of aerosols. An aerosol is a suspension of a solution in air and may be conveniently produced by the passage of a current of compressed air or oxygen through a nebulizer containing the solution. Bryson stated: "It is known that the behavior of particulate substances in inspired air is a function of their size; effective penetration of the small bronchioles and alveolae is best attained by small particles." [14] Krueger and others,[15] working with monkeys and mice and using india ink and radioactive chromic phosphates as indicators, demonstrated that inhaled material is uniformly distributed and penetrates to the outermost air sacs of the lungs.

Bryson and his co-workers at the Carnegie Foundation [14] were the first to suggest the use of penicillin by inhalation. They investigated this possibility and found that the nebulization of a buffered solution of penicillin with a standard glass nebulizer (De Vilbiss no. 40) produces an aerosol with particles of an average size of 0.5 micron when the rate of flow of compressed air is 5 liters per minute. They concluded that "rate of air flow through the nebulizing apparatus and physical properties of the solution are two factors influencing particle size." Since Van Wijh [16] had demonstrated that between 50 and 80 per cent of inhaled dust particles of the same size as penicillin aerosol are retained in the human respiratory tract, Bryson concluded that large amounts of penicillin could be introduced into the lungs by the aerosol method. He also performed a series of experiments showing that aerosolization of a solution of penicillin did not decrease its antibacterial activity, that inhaled penicillin could be recovered from the lungs of rabbits and, finally, that nebulized penicillin diffuses into the blood stream.

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12. Stacey, J. W.: Inhalation of Nebulized Solutions of Sulfonamides in the Treatment of Bronchiectasis, Dis. of Chest **9**:302-306 (July-Aug.) 1943.

13. Barach, A. L.; Molomut, N., and Soroka, M.: Inhalation of Nebulized Promin in Experimental Tuberculosis: Sodium P,P'-Diamino-Diphenylsulfone-N,-N'-Didextrose Sulfonate, Am. Rev. Tuberc. **46**:268-276 (Sept.) 1942.

14. Bryson, V.; Sansome, E., and Laskin, S.: Aerosolization of Penicillin Solutions, Science **100**:33-35 (July 14) 1944.

15. Prophylaxis and Treatment of Experimental Influenza by Inhalation of Immune Serum, Personnel of Naval Laboratory Research Unit no. 1, Univ. Calif., Berkeley, Calif., abstracted, Federation Proc. **2**:101, 1043.

16. Van Wijh, A. M., and Patterson, H. S., cited by Bryson, Sansome and Laskin.[14]

Barach and his collaborators [7] were the first to apply this method of administering penicillin therapeutically. They carried out a series of investigations on both animals and human subjects and clearly demonstrated the clinical efficacy of penicillin aerosol in some cases as well as the lack of irritating and toxic effects. Numerous determinations of the level of penicillin in the blood were made following the inhalation of the drug; the levels were found to be low, averaging between 0.01 and 0.04 Oxford unit per cubic centimeter. Most of the patients so studied were suffering from chronic asthma, and it was also shown that the passage of penicillin from the lungs to the blood stream is affected by the degree of pulmonary pathologic change. These authors stressed the point, however, that the aim of this method of treatment is not to obtain a high blood level of penicillin but rather to achieve a high local concentration on the surface of the bronchial mucosa. They were also able to recover 10 to 20 per cent of the penicillin given by aerosol nebulization from the urine of their patients. Both Bryson and Barach demonstrated that the condition of the respiratory passages plays an important role in the absorption of the aerosol from the bronchi, for they showed that a normal person who inhales deeply and holds his breath for a few seconds may excrete as much as 60 per cent of the inhaled penicillin in the urine; a person with chronic inflammatory changes in the lung cannot inspire as deeply nor hold his breath as long and consequently will absorb and excrete less of the inhaled material.

Methods of Administration.—The technical problems involved in treating infants and children with penicillin by inhalation differ from those encountered with adults mainly in that little cooperation can be expected from children under the age of 4 or 5 years. Appropriate modifications in the methods of administration are accordingly required. The first type of apparatus used consisted of a nebulizer [17] connected on one side with an oxygen tank and on the other with a no. 10 French catheter; the latter was inserted through the nose into the oropharynx, its tip resting just behind the uvula. Between the nebulizer and the catheter was placed a 250 cc. Erlenmeyer flask, to constitute a trap for the larger particles of penicillin in order to prevent their condensation in the catheter, with resulting obstruction. The oxygen was kept flowing at a rate of 3.5 to 4 liters per minute, and the solution was prepared so as to contain the total dose of penicillin in 1 cc. of isotonic solution of sodium chloride. In order to recover the penicillin which had condensed on the sides of the nebulizer, this 1 cc. of solution was followed by 1 cc. of normal isotonic solution of sodium

17. Nebulizer made by the Vapoephrin Co., Upper Darby, Pa.; O. E. M. Meter Mask, made by the Oxygen Manufacturing Co., New York.

chloride. The treatments were given four times daily, and the nasal catheter was removed after each treatment unless continuous oxygen therapy was also required.

Improvement of the pulmonary infection was obtained in 3 of 4 patients by this method. However the mechanical difficulties encountered with small children in passing a nasal catheter several times a day and the exhaustion from the associated struggles soon made it clear that a less traumatic way of administering aerosol should be sought. Experiments were then carried out with various types of masks. An ordinary anesthesia mask with a solid metal mouthpiece was first tested. This was connected with the nebulizer by means of a rebreathing bag in order to recover for use some of the exhaled penicillin. This method eliminated most of the previously mentioned inconveniences and was well tolerated by most of the patients. The use of this mask permitted an increase in the flow of oxygen to 5 to 6

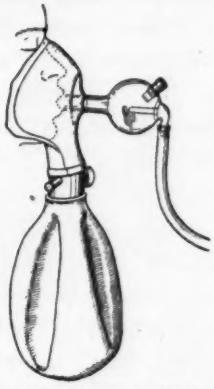

Fig. 1.—Apparatus for administering penicillin aerosol, consisting of rubber mask [17] with rebreathing bag and nebulizer.[17] The vapor is produced by a flow of oxygen into the nebulizer at the rate of 5 to 6 L per minute.

liters a minute, giving the double advantage of better nebulization and shorter duration of the treatments. Two disadvantages were observed. Even though an opening existed on the side of the mask, the system was almost a closed one, resulting in an excessive accumulation of carbon dioxide; it was therefore necessary to interrupt the treatment for a breathing spell every three or four minutes. Also, large amounts of penicillin were lost by condensation in the rebreathing bag, which seemed rank extravagance when penicillin was obtained with so much difficulty.

An oxygen mask of soft rubber has been used in all recent experiments.[17] In this type of apparatus the open end of the nebulizer is inserted directly through the mask to the lips of the patient (fig. 1). One cubic centimeter of isotonic solution of sodium chloride containing

the prescribed amount of penicillin is placed in the nebulizer, and the stream of oxygen is permitted to flow at the rate of 6 liters a minute. The duration of the individual treatments is eight to twelve minutes. A rebreathing bag is connected with the mask in order to utilize some of the penicillin in the expired air; all other openings of the mask are plugged. The oxygen mask which we have used, the O. E. M. Meter Mask,[17] comes only in adult size, but being very flexible it can be adapted to children over 1 year of age. The fit is of course imperfect, but the loss of aerosol is counterbalanced by the advantage of losing some of the accumulated carbon dioxide.

This type of oxygen mask and nebulizer apparatus has been well tolerated by all patients over the age of 18 months on whom it has been used and by many who are between 12 and 18 months. Once the initial anxiety has been overcome and the children have become accustomed to the procedure, an amazing degree of cooperation is obtained. Little success has been achieved in attempts to administer penicillin by inhalation to infants under 1 year of age. For both technical and psychologic reasons it seems advisable to give the drug by some other channel to this age group. Some of the apparatus described by Barach for use with adults[7] can be applied to the treatment of children over 4 or 5 years of age.

Doses.—The amounts of penicillin administered by inhalation have varied considerably. The doses have not been calculated on a unit per weight basis, but standard doses have been used regardless of the age of the patients. All patients were between the ages of 1 and 6 years. During the first few months of the present study the total amount of the drug given by aerosol nebulization in each twenty-four hour period averaged around 32,000 Oxford units distributed in four doses. As the supply of penicillin improved, the doses were increased and also the number of treatments per day. Recently it has been our practice to give 20,000 units each time, the inhalations being repeated seven times a day, resulting in a total dose of 140,000 units in twenty-four hours. The treatments are given every three hours, with the exception of one omission during the night to give a six hour rest period. When patients are given intramuscular and aerosol therapy concurrently, the injections are given every three hours eight times a day, making a total of 160,000 units by this route per day and a grand total of 300,000 units per day by both methods. In a few cases a continuous intramuscular drip of 200,000 units a day has been given in place of the eight injections.

The length of the courses of treatment has also varied. In the earlier experiments, treatment was given for a period of five to eight days and this was followed by a rest period of comparable length.

More recently the period of treatment has been ten to fifteen days, with a subsequent rest period of two to four weeks. The latter plan has on the whole proved more satisfactory.

Toxicity.—No toxic symptoms ascribable to the administration of penicillin either by intramuscular injection or by inhalation have been observed, and in no instance has there been evidence of sensitization to this drug. There has been a complete lack of evidence of irritation of the respiratory tract in the children receiving the higher doses of penicillin aerosol. It should be noted that in Barach's opinion the penicillin powder should be dissolved in sterile isotonic solution of sodium chloride rather than in distilled water because distilled water appears to be irritating to the bronchial mucosa when administered by inhalation. The aerosol treatments are much better tolerated than the intramuscular injections, which are painful and lead to chronic apprehension and an acute fear of any uniformed person who approaches the bed.

In a few instances there were periods of unexplained fever shortly after the commencement of therapy, the temperature usually falling after a day or two. The general condition of the patients was, as a rule, not affected by this period of hyperpyrexia, and it was assumed that the fever was due to the sudden destruction of large numbers of pathogenic organisms, with the liberation of pyrogenic substances. This hypothesis is substantiated by the demonstration by Kirby and others [18] of the lytic action of penicillin on organisms of the staphylococcus group.

RESULTS OF TREATMENT WITH PENICILLIN AEROSOL ALONE OR IN COMBINATION WITH INTRAMUSCULAR ADMINISTRATION OF PENICILLIN

Ten patients with congenital pancreatic deficiency and associated chronic pulmonary infection were treated with penicillin aerosol during the period between July 19, 1944 and May 31, 1945. To 4 subjects the penicillin was administered exclusively by inhalation (cases 8, 9, 10 and 13). To 6 subjects the drug was given by both intramuscular and inhalation routes. However, 4 of the latter group received aerosol alone during the first courses of treatment (cases 6, 7, 11 and 12). These patients have now been followed for periods of six to fifteen months after the initial therapy with penicillin aerosol. Conclusions as to the efficacy of the inhalation therapy must be based primarily on analysis of the results which were obtained when this was the only method by which pencillin was administered.

18. Kirby, W. M. M.: Bacteriostatic and Lytic Actions of Penicillin on Sensitive and Resistant Staphylococci, J. Clin. Investigation **24**:165-169 (March) 1945.

For the purpose of discussion the 10 cases can be divided into two groups in accordance with the therapeutic success achieved. Group A includes 5 patients (cases 7, 8, 9, 13 and 14), in all of whom very

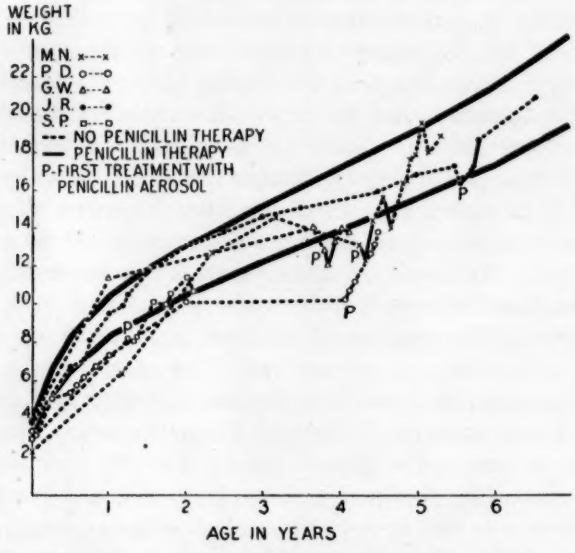

Fig. 2.—Weight curves of 5 patients who showed a prompt and enduring response to therapy with penicillin aerosol. The heavy lines indicate a range of weight of two thirds that of normal children.

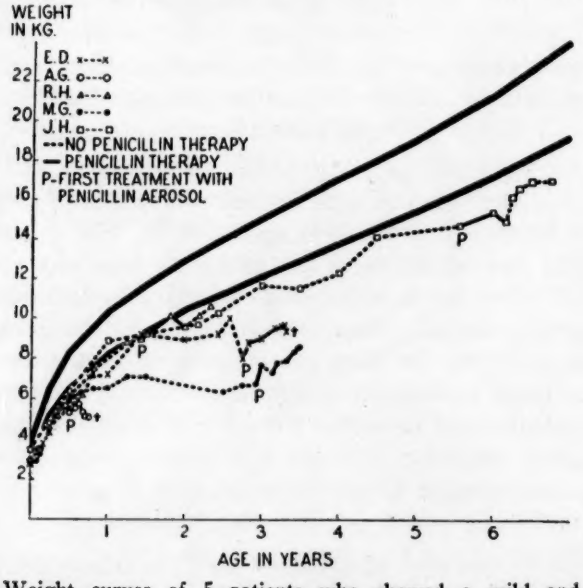

Fig. 3.—Weight curves of 5 patients who showed a mild and transitory response to penicillin aerosol. The heavy lines indicate the range of weight of two thirds that of normal children.

satisfactory and so far enduring results were obtained (fig. 2). .Group B consists of 5 patients, (cases 6, 10, 11, 12 and 15) who benefited by penicillin therapy but in whom improvement was only slight or moderate and was transitory (fig. 3).

In the study of the patients of group A, those who showed a good response to penicillin, it will be seen that patients 7, 13 and 14 showed a number of striking similarities in their course prior to admission and in their response to treatment. The 3 children were in the same age group, their ages on admission to the hospital being 4 years and 3 months, 3 years and 11 months and 4 years and 1 month respectively. Despite the fact that a diagnosis of pancreatic disease had never been made and that they had never received any dietary treatment, these youngsters had grown and developed normally until a few months prior to their admission to the hospital, when a chronic cough had developed following an acute infection of the upper respiratory tract. The duration of the pulmonary symptoms prior to their admission was seven, eight and twenty-four months respectively. In each of these cases at the time of admission there was severe respiratory embarrassment with cyanosis, frequent coughing and suprasternal and intercostal retractions. Physical and roentgenologic signs of severe pulmonary disease were noted.

It has been our repeated experience in cystic fibrosis of the pancreas that when pulmonary suppuration accompanied with cyanosis sets in death is not far off. The favorable response of these 3 patients to the administration of penicillin aerosol was made more dramatic by the knowledge that if they went untreated only a few weeks of life lay ahead of them. After treatment there was a drop in the leukocyte count, the temperature returned to normal limits, the respiratory symptoms regressed and there was a striking gain in weight (fig. 4). These gratifying results have been enduring. All 3 patients were readmitted for further treatment, but their general course has been steadily uphill. At the date of writing all 3 children are wholesome, happy youngsters leading a normal life, except for strict dietary supervision. In case 7 the patient, first treated a year ago, has not had a chronic cough for some months, while the other 2, who have been treated more recently, retain a mild and infrequent cough; physical signs of pulmonary infection have disappeared in all and clubbing of the fingers has decreased or disappeared. Roentgenologic examination still shows increased bronchovascular markings, which we interpret as irreversible or slowly reversible changes due to scarring. In case 7 the decrease in pulmonary emphysema is especially striking, with a return of the thoracic contours toward the normal ones. The circumference of the thorax has decreased in spite of the child's normal gain in height and weight. It should be mentioned that in the first

2 cases there was a response to penicillin given by aerosol nebulization alone, while, in the third case, the patient, who received the drug both by aerosol nebulization and by continuous intramuscular drip, responded somewhat more promptly; progress attained at the end of the first month following the beginning of therapy was approximately the same.

The 2 remaining patients in group A (cases 8 and 9) had a much less severe infection. In both cases a diagnosis of fibrocystic disease of the pancreas had been made prior to the present admission and both patients had been receiving the diet for pancreatic deficiency.[2] Patient 8, a girl of 15 months, has received dietary therapy for about six months and patient 9, a girl of 6 years, since early infancy. The latter patient has previously been given as an illustration of the effect of discontinuing dietary therapy.[2] Her progress was excellent until

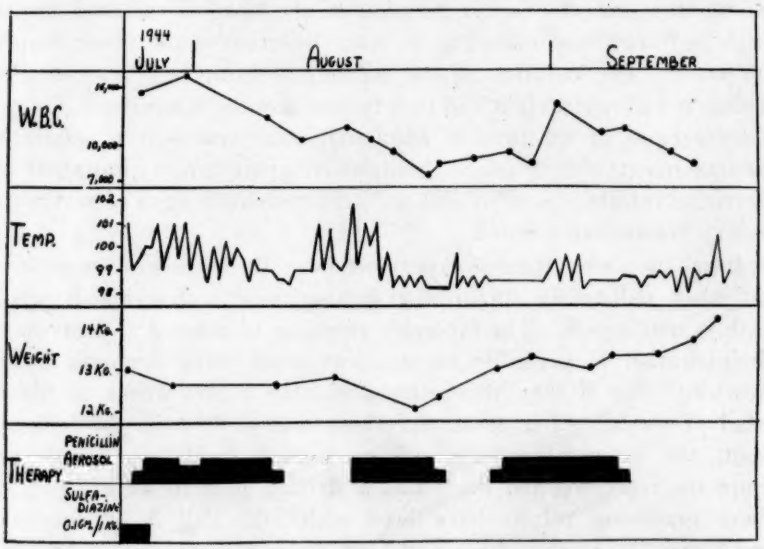

Fig. 4.—Chart of temperature, weight and leukocyte counts, showing response of M. N. (case 7 [S 29]) to therapy with penicillin aerosol.

the age of 4 years, when pancreatic extracts were discontinued and other lapses in the regimen took place. The rate of growth decreased, and finally a few months before admission a chronic cough appeared. At the time of her admission there were slight dyspnea and mild cyanosis during paroxysms of coughing; numerous moist rales could be heard on auscultation of the lungs, and roentgenograms of the chest showed evidence of a moderately advanced chronic bronchopneumonia.

Two courses of penicillin aerosol were given to each of these 2 children with satisfactory results. In patient 8 the respiratory symptoms all but disappeared within a period of a few weeks, and a roentgenogram of the chest taken two months after discharge failed to reveal evidence

of abnormality. The improvement has continued to date, even though further therapy had to be given in another hospital because of an increase in the frequency of the cough. Patient 9 gave a most satisfactory response. Within four weeks all symptoms had disappeared, and at two months the pulmonary fields were almost completely clear as shown by a roentgenogram. The child had several colds during the last winter without sequelae and has remained so well that she has not returned for further treatment; she has been regularly at school and has been normally active.

Group B includes 5 patients (cases 6, 10, 11, 12 and 15) who responded to penicillin therapy but in whom improvement was only slight and of short duration (fig. 3). Two of these children (cases 11 and 12) presented similarities in the clinical picture and the response to therapy. The ages of these two girls on admission were 2 years and 6 months and 2 years and 9 months respectively. Both were acutely and chronically ill and extremely retarded in growth and development. Both had failed to do well or to gain weight normally from the first weeks of life and had had bulky foul stools from infancy. The usual signs of severe respiratory disease were present, although the duration of the respiratory symptoms was different in the 2 cases; one of the patients (case 11) had had a cough since the age of 6 months, whereas in the other patient (case 12) a cough was first noted two months before her admission to the hospital. Decided improvement followed the first course of penicillin in both cases. The leukocytosis of the latter patient (case 12), however, was unaffected. Within a few weeks after the end of the first course of therapy the symptoms recurred, and after subsequent courses of treatment there was little or no further gain in weight or decrease of the cough. One of these children is now ambulatory and fairly comfortable but has a severe productive cough and shows little gain. The other (case 12) has recently died after an acute exacerbation of symptoms, eight months after her first admission and her first course of therapy. In this case the strain of staphylococci obtained from the nasopharynx prior to therapy was sensitive to penicillin in vitro, but several cultures obtained after the first course of therapy and also the postmortem cultures grew staphylococci which showed increased resistance. This increased resistance of the organism may explain why the initial improvement proved transitory.

Another patient (case 6) was first seen at the age of 8 months, when the diagnosis of pancreatic deficiency was first made. His cough had appeared at the age of 2 months, and roentgenograms taken at that time had demonstrated patches of atelectasis, which have since remained constant. During the nearly two years since he was first seen he has continued to have a chronic productive cough and moderate

retardation in growth. Penicillin aerosol was first given to him at the age of 16 months, with striking initial improvement which proved transitory, and subsequent courses of therapy have had little effect. His case thus resembles the previous 2 cases except that his pulmonary infection has never been as severe nor his development as much retarded.

A 6 year old girl (case 10) had had a history of bulky, fatty stools since early in life. She had done fairly well from the second to the fifth years on a regimen for patients with celiac disease. For the ten months prior to admission to the Babies Hospital the patient had been on an unrestricted diet following a mistaken diagnosis of congenital megacolon (Hirschsprung's disease) made at another hospital. During this period there had been no gain in weight, and a productive cough made its appearance. When first seen the child was not acutely ill but noticeably underdeveloped and undernourished. Physical examination of the lungs revealed nothing abnormal, but roentgenologic evidence of chronic inflammatory changes were found. Several courses of penicillin aerosol were given at different times, but only slight improvement was registered. There was no further progress of the pulmonary infection, but the chronic cough persisted. The lack of response of this child is at variance with our previous experience, for children with a late onset of infection of the respiratory tract have usually responded promptly to treatment.

Case 15 was that of a 6 month old baby with a history of abnormal stools and a lack of gain in weight since birth. A severe infection of the respiratory tract had been present since the age of 2 months, and when the patient was first seen he was found to be critically ill, with signs of extensive involvement of the lungs. Penicillin was administered intramuscularly in large doses and also for a short time by aerosol nebulization. Improvement was noted following administration of penicillin, but it was only slight and of few weeks' duration. In spite of repeated courses of penicillin both by inhalation and by parenteral injection, the pulmonary infection again became progressive, and at the end of the third month of stay in the hospital the patient died. Unfortunately, no bacteriologic data are available for this patient. The lack of satisfactory response to therapy in this infant strengthened our impression that the prognosis of patients showing evidence of infection of the respiratory tract during the first month or two of life is still poor despite the chemotherapeutic methods available.

A complete regression of all the symptoms within a few days after the beginning of penicillin therapy has never been obtained, even in patients who responded to treatment. While the early results of decrease of cough and loss of cyanosis and the disappearance of the "snowflake" shadows in the lungs were frequently dramatic by the second week, the greatest improvement was usually found some weeks

after the drug was discontinued. In many instances symptoms recurred after three or four weeks and steady progress was obtained by giving repeated courses of treatment whenever an exacerbation of coughing was evident.

Roentgenograms of the lung taken during the terminal stages of the infection of the respiratory tract show diffuse focal "snowflake" shadows similar to those of disseminated pulmonary tuberculosis. These shadows disappear rapidly with the institution of penicillin therapy in all cases in which there is a good clinical response, whether the penicillin is given by aerosol nebulization or intramuscularly (fig. 5). The increase in bronchovascular markings may remain for many months, even after complete disappearance of pulmonary symptoms, and then a gradual regression occurs. Their persistence seems to bear a relationship to the duration of pulmonary symptoms prior to therapy. They are interpreted as the result of irreversible or slowly reversible

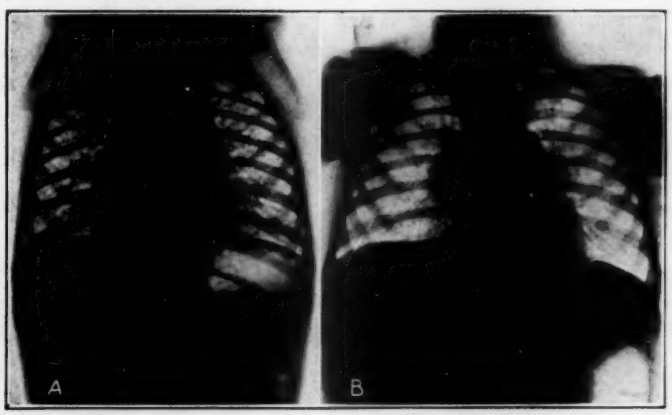

Fig. 5.—*A*, roentgenogram of the chest of M. N. (case 7 [S 29]) before penicillin therapy showing diffuse "snowflake" lesions of the lung and hilar shadows. *B*, Roentgenogram of the chest after penicillin aerosol therapy, taken four and one-half months after roentgenogram shown in figure 5 *A*. The diffuse lesions have disappeared. The hilar shadows are reduced but still present.

changes due to scarring. This interpretation is strengthened by the finding of increased fibrous tissue in the bronchial walls on postmortem examination. The mild diffuse tubular bronchiectasis found at postmortem examination cannot readily be distinguished by roentgenogram from the lesions of active chronic infection or from those of an inactive lesion with scarring.

In cases of a milder infection of relatively short duration (cases 8 and 9) the roentgenographic appearance of the lung has become completely normal after treatment. It seems probable that in some of the patients who responded to therapy after prolonged infection the roentgenograms will also show clearing after more time has passed,

as has been the case with a few of the patients who have responded to dietary therapy alone.[2]

BACTERIOLOGY

Hemolytic Staph. aureus, fermenting mannitol and coagulase positive, was isolated either in pure culture or as the predominating organism from the lungs of 11 of the 12 patients from whom materials for culture were obtained post mortem from the lung (table 1) and by puncture of the lung from 2 living patients. This supports the conclusion [3] that Staph. aureus is the usual etiologic agent in the suppurative bronchopneumonia of patients with cystic fibrosis of the pancreas.

Materials for culture were repeatedly taken from the nasopharynx of each subject during the course of the present investigation. In almost all instances a mannitol-fermenting and coagulase-positive hemolytic Staph. aureus, was found in large numbers or as the only pathogenic organism present. In a few cases, however, strains of hemolytic Staph. aureus which differed in their action on mannitol and in their coagulase activity were found either in the same culture or on different occasions. Frequently no growth was obtained on cultures of material from the nasopharynx taken soon after the administration of penicillin aerosol.

Titrations of the sensitivity of the organisms to penicillin were carried out in 13 cases at various intervals during the course of the infections. Two serial dilution methods of titration were used.[19] For the most part the materials for culture were obtained from the nasopharynx. In cases 1 and 2 punctures of the lung were done, while in case 3 material was obtained from the trachea through a tracheotomy tube. In cases 4 and 12 the organisms were isolated from the nasopharynx prior to death and from the lungs at autopsy. The results are recorded in table 4. It is evident that in the majority of cases the strains of staphylococci were inhibited in vitro by concentrations of penicillin of 0.1 unit per cubic centimeter or less. A great deal of variability was observed in the response to penicillin of the staphylococci from the same patients on different occasions, a fact which has been previously noted by others. In 3 cases (cases 2, 4 and 12) a definite increase in the resistance of the organisms to the drug was noted following therapy. An increase of resistance was also observed in case 6, but it is apparent that various strains of Staph. aureus were present in this patient and that each showed a different degree of resistance to penicillin. Clincally this child showed only a slight response to therapy.

19. Foster, J. W., and Woodruff, H. B.: Microbiological Aspects of Penicillin: I. Methods of Assay, J. Bact. **46**:187-202 (Aug.) 1943. Dawson, M. H.; Hobby, G. L., and Lipman, M. O.: Penicillin Sensitivity of Strains of Non-Hemolytic Streptococci Isolated from Cases of Sub-Acute Bacterial Endocarditis, Proc. Soc. Exper. Biol. & Med. **56**:101-102 (June) 1944.

20. Footnote deleted on proof.

TABLE 4.—*Sensitivity to Penicillin of Strains of Hemolytic Staph. Aureus Isolated from Patients with Fibrocystic Diseases of the Pancreas and Suppurative Bronchopneumonia*

Case No.	Date	Source	Fermentation of Mannitol	Coagulation of Serum	No. of U/Cc. of Penicillin Necessary to Inhibit Drug	Result of Therapy
1*	4/28/43	Nasopharynx	+	+	As sensitive as standard strain	Excellent response to therapy; death on recurrence when penicillin was no longer available
2*	6/12/43	Lung (by puncture)	+	+	Half as sensitive as standard strain	Good response to first course of treatment
	8/27/43	Lung (by puncture)	+	+	Completely resistant	No response to second course
3	2/24/44	Trachea (through tracheotomy tube)	+	+	0.13	Good response at first
	3/16/44	Trachea	?	?	0.26	Death when penicillin was no longer available
4	10/12/44	Nasopharynx	+	+	>26.20	No response to treatment
		Lung (at autopsy)	+	—	250.00	
6	7/26/44	Nasopharynx	+	+	0.13	Only slight and transient improvement
	10/25/44	Nasopharynx	—	—	26.2	
	1/18/45	Nasopharynx	+	+	0.04	
	2/20/45	Nasopharynx	+	—	10.00	
	3/20/45	Nasopharynx	+	—	4.00	
7	7/26/44	Nasopharynx	+	+	0.06	Pronounced and continued improvement
	11/ 2/44	Nasopharynx	+	+	0.04	
	11/ 8/44	Nasopharynx	—	—	0.10	
	11/ 9/44	Nasopharynx	—	—	0.30	
	11/11/44	Nasopharynx	—	—	0.10	
	11/21/44	Nasopharynx, colony 1	—	—	0.40	
		colony 2	—	—	0.40	
	11/28/44	Nasopharynx, colony 1	—	—	0.01	
		colony 2	+	+	0.05	
		colony 3	+	+	0.04	
		colony 4	—	—	0.04	
	1/ 8/45	Nasopharynx	—	—	0.20	
	2/14/45	Nasopharynx	—	—	0.08	
	4/ 5/45	Nasopharynx	—	—	0.06	
8	10/ 4/44	Nasopharynx	+	+	0.13	Pronounced and continued improvement
	10/25/45	Nasopharynx	+	+	0.13	
9	10/10/44	Nasopharynx	+	+	>26.20	Excellent response to therapy
	10/21/44	Nasopharynx	+	+	>26.20	
	10/31/44	Nasopharynx	+	—	0.05	
10	11/15/44	Nasopharynx, colony 1	+	+	0.08	Only slight improvement
		colony 2	+	+	0.08	
	1/ 3/45	Nasopharynx	+	+	0.50	
11	11/15/44	Nasopharynx, colony 1	+	+	0.10	Some improvement with frequent recurrences
		colony 2	+	+	0.10	
12	12/15/44	Nasopharynx, colony 1	+	+	0.10	Some improvement during therapy; recurrence each time after discontinuing penicillin
		colony 2	+	+	0.10	
	12/26/44	Nasopharynx, colony 1	+	+	1.00	
		colony 2	+	+	2.00	
		colony 3	+	+	2.00	
	1/ 3/45	Nasopharynx	+	+	1.00	
	1/18/45	Nasopharynx	+	+	2.00	
		Right lung, lower lobe, colony 1	+	+	10.00	
		At autopsy, left lung, lower lobe, colony 2	+	+	10.00	
13	.....	Nasopharynx, colony 1	+	+	0.04	Pronounced improvement
		colony 2	+	+	0.04	
14	.....	Nasopharynx, colony 1	+ (?)	+ (?)	0.04	Pronounced improvement
		colony 2	+ (?)	+ (?)	0.10	
		colony 3	+ (?)	+ (?)	0.10	

* Some of the records concerning cases 1 and 2 were lost, and the definite amounts of penicillin necessary to inhibit these three strains of Staph. aureus cannot be reported. The standard strain referred to was a hemolytic streptococcus (C203 MV).

The response to therapy correlated well with the in vitro sensitivity of the organisms to penicillin in 10 of 13 cases. In cases 11 and 12 only slight and transient improvement was obtained, even though strains of staphylococci isolated from the nasopharynx were sensitive to penicillin. In case 9 the therapeutic result was excellent, despite the findng of penicillin-resistant organisms in the upper respiratory tract on two occasions. While the poor general condition and the duration of the infection prior to therapy may have played a part in the lack of response in case 11, it seems probable that in cases 9 and 10 the organisms isolated from the nasopharynx did not belong to the strain causing the pulmonary infection. Staph. aureus is a common saprophyte in the throats of children. The pathogenic organisms from the bronchi must also be present in the throat, in view of the constant coughing up of infected material. The colonies of saprophytes and pathogens cannot be readily differentiated, and it is therefore possible that when only one or a few colonies are tested for sensitivity they may not represent the infective agent. Consequently, insensitivity to penicillin of the strains of staphylococci isolated from the nasopharynx of a patient cannot be considered as proof that the patient will not give a good clinical response to penicillin therapy, and the therapeutic test should be made. However, clinical results corresponded with the bacteriologic findings in such a high percentage of cases that the assumption is justified that the most important factor affecting the clinical outcome is the sensitivity of the infecting organisms to penicillin.

COMMENT

Penicillin is the first drug known to affect the course of fibrocystic disease after cyanosis has marked the existence of suppurative staphylococcic bronchitis. These cases, therefore, present an unusual opportunity for evaluation of the methods of administration of the drug in the treatment of pulmonary infection. The use of penicillin by inhalation is peculiarly adapted to the circumstances obtaining in this disease. Excellent success has resulted in 5 of the 10 cases of the present series in which penicillin aerosol was used. The limitations are chiefly two: the fact that some strains of staphylococci are or may become resistant to the drug and the technical difficulties encountered in giving aerosol to patients under 1 year of age.

Our experience with the use of penicillin alone given intramuscularly is limited not only by the small number of patients who were so treated but also by the fact that 3 of the 5 patients were seen when supplies of the drug were inadequate. The 1 survivor is definitely a therapeutic success.

Rapid improvement has been obtained with penicillin aerosol alone and with the administration of penicillin aerosol and by intramuscular

injection of the drug simultaneously. The use of aerosol is in reality a special instance of topical application of the drug, comparable to intrathecal administration in meningitis. The results of therapy are out of proportion to the blood levels obtained, which are usually low. It is therefore reasonable to give inhalation and intramuscular therapy concurrently in cases in which bacteremia or parenchymal pulmonary involvement are present or suspected. However, penicillin alone has proved adequate when symptoms are less severe and is preferred when feasible because of the psychic trauma which accompanies frequent painful injections.

The optimal dose of penicillin is still unknown. Of the 2 patients who showed the most dramatic recovery, 1 received 32,000 units per day by inhalation alone and the other was given a total of 340,000 units daily, of which 140,000 units was given by aerosol nebulization and the remainder by continuous intramuscular drip. Kirby [18] has expressed the belief that for each case there is an optimal dose beyond which less satisfactory results are obtained. This conclusion is based on the observation that, while penicillin has both bacteriostatic and lytic effect on Staph. aureus, lysis can occur only when the organisms are multiplying. In vitro an optimal level can be found at which all organisms are destroyed within twenty-four hours. From a practical standpoint the optimal dose is difficult to determine in vivo. The unhappy experience in the first few cases of the present series, when scarcity of the drug necessitated low doses, has influenced us to give generous amounts now that it is possible. We are further impelled to the use of large doses by the knowledge that the staphylococci may develop resistance to penicillin when exposed to sublethal doses.[21]

Acute pharyngitis and its complications ordinarily respond to sulfadiazine. On the other hand, penicillin aerosol in our experience as in that of others [22] has not been effective in the control of acute infections of the upper respiratory tract or of their complications, such as otitis media and sinusitis. It is logical to expect that penicillin aerosol should be ineffective because the nebulin cannot directly penetrate the middle ear or the openings of paranasal sinuses obstructed by mucus or congested mucous membranes and adequate blood levels cannot readily be obtained by this means. In addition, experience has shown that some patients become unresponsive to penicillin. It therefore seems discrete to reserve this drug for occasions when

21. Demerec, M.: Production of Staphylococcus Strains Resistant to Various Concentrations of Penicillin, Proc. Nat. Acad. Sc. **31**:16-24 (Jan.) 1945.

22. Meads, M.; Flipse, M. E.; Barnes, M. W., and Finland, M.: Penicillin Treatment of Scarlet Fever: Bacteriological Study of the Nose and Throat of Patients Treated Intramuscularly or by Spray with Penicillin and a Comparison with Sulfadiazine, J. A. M. A. **129**:785-789 (Nov. 17) 1945.

the need for it is clear. In particular, the use of small doses of penicillin administered by atomizer for the treatment of infections of the upper respiratory tract is inadvisable.

The outcome of penicillin therapy is affected not only by the sensitivity of the infective organism and the method of therapy but also by the age and general condition of the patient. The child who has had little or no retardation of growth during early life and in whom respiratory symptoms have developed after the age of 6 months usually responds favorably to chemotherapy, as he does to dietary therapy[2] (fig. 2). Most of the infants who give evidence of nutritional and respiratory difficulty during the first month or two of life still have a poor prognosis, though a few respond to treatment (fig. 3). The basic reason for the failure of therapy in cases with early onset may be found when the susceptibility of the patients to infection by staphylococci is explained and the cause of the variations in severity of the disease is known.

SUMMARY AND CONCLUSIONS

The respiratory infection associated with cystic fibrosis of the pancreas has been described with respect to the clinical course and the pathologic and bacteriologic conditions. The clinical course is marked by a more or less prolonged period of chronic cough, with exacerbations following intercurrent infections. This phase is followed by a period of cyanosis and respiratory distress of several weeks' duration, terminating in death. At postmortem examination the characteristic lesion is a chronic inflammation and fibrosis of the small and middle-sized bronchi, with a superimposed acute suppurative bronchitis due to hemolytic Staph. aureus. The symptoms of asphyxia result from occlusion of the bronchi and trachea by mucopurulent material.

Drugs of the sulfonamide group are of value in the prophylaxis and treatment of intercurrent infections of the upper respiratory tract but are ineffective after the stage of suppurative bronchitis has been reached.

Penicillin may be effective in treatment of the infection of the respiratory tract after the appearance of respiratory distress and cyanosis. Failure in therapy may occur in cases in which the patient is infected with an organism which is resistant to the drug. The most satisfactory method of administering penicillin to patients with this disease is by inhalation alone (penicillin aerosol) or by inhalation in combination with intramuscular injection of the drug. Methods of giving penicillin aerosol to patients over the age of 1 year have been described. These have proved to be safe, practical and effective. Inhalation of penicillin aerosol is viewed as a special case of topical treatment, and intramuscular injection should be used in combination with it when bacteremia or involvement of the parenchyma of the lung is suspected. Aerosol

therapy alone is effective in cases of mild attacks and in some severer attacks.

Factors influencing the response of these patients to penicillin therapy have been discussed. The chief of these are adequate doses and repetition of therapy as required, the susceptibility of the organisms to penicillin and the general nutrition and development of the patient. A late onset of respiratory symptoms, good general development and previous dietary therapy are to the patient's advantage.

The mortality of fibrocystic disease has been reduced, and an increasing number of patients have been maintained in good health and in a state of normal nutrition and activity. This has been accomplished by the following means: (*a*) an appropriate diet, begun promptly and continued consistently; (*b*) the use of sulfadiazine during the stage of chronic cough, both for prophylaxis and for treatment of intercurrent infections, and (*c*) the use of penicillin either by inhalation alone or by inhalation combined with intramuscular injection for the treatment of the terminal suppurative bronchitis.

REPORT OF CASES

CASE 1.—J. A. (S 18),[23] a 7 week old white boy, was admitted to Babies Hospital on March 8, 1943, with a history of projectile vomiting after each feeding for over a month. The amounts vomited each time were said to have been large, and several different formulas and feeding schedules were tried to no avail. At the same time five or six large, yellow, foul-smelling stools were being passed each day. On physical examination the baby appeared to be quite vigorous but extremely thin. The weight on admission was 3,300 Gm., a full 500 Gm. below the birth weight. The abdomen was considerably distended; no peristaltic waves were visible, and no masses were palpable. The lungs were clear on auscultation and percussion. On the basis of the history and the physical examination, the patient was thought to present a simple feeding problem. An evaporated milk formula was prescribed, and after nine days in the hospital the baby was discharged apparently improved.

The vomiting ceased to be a problem; but soon after discharge a frequent, paroxysmal, nonproductive cough made its appearance. On readmission on March 20, two weeks after the previous discharge, the baby was found to be in poor physical condition. There had been no gain in weight for some time, and the infant appeared pale and emaciated, with flat buttocks and a prominent abdomen. Coughing was frequent, and during paroxysms the child became dyspneic and cyanotic. A few crackling rales could be heard over the pulmonic areas. The rest of the physical examination was noncontributory. A roentgenogram of the chest taken on April 2, failed to reveal any evidence of pathologic changes. A tentative diagnosis of cystic fibrosis of the pancreas was made, and this was later substantiated by the results of duodenal drainage. The child was then placed on a low fat high protein diet. On April 12, the temperature, previously normal, suddenly rose to 101.5 F. and daily spiked up to 102 F. for several days. There

23. Case numbers preceded by S refer to the serial number of cases with fibrocystic disease of the pancreas seen at Babies Hospital since 1939 and correspond to the case numbers in other papers of this series.

was a change for the worse in the child's condition, as was evidenced by increased coughing and persistent cyanosis. A roentgenogram of the chest revealed the presence of several large shadows of increased density in the lungs, which were thought to be caused by pulmonary abscesses. The white blood cell count, previously around 10,000 per cubic millimeter, rose on April 26 to 16,000, with 70 per cent polymorphonuclear leukocytes. A puncture of the lung was done on April 20, and a pure culture of hemolytic Staph. aureus (mannitol fermenting and coagulase positive) was obtained. The same organism was recovered from a culture of materials from the nose on the same day, while a culture of blood was positive for a hemolytic Staph. aureus (mannitol fermenting and coagulase positive). The bacteria obtained from the puncture of the lung were found to be as sensitive to penicillin as the standard laboratory strain of hemolytic streptococci. Penicillin therapy was started on the same day, April 20, and was continued for thirty-three days, until May 22. A total of 624,000 units of penicillin, with an average of 20,000 units in twenty-four hours, was administered by intramuscular injections. Striking improvement was almost immediately noted clinically and by roentgenogram. The improvement continued after the administration of penicillin was stopped, although an occasional cough persisted. On June 30 a roentgenographic examination of the chest failed to reveal any evidence of pathologic changes. On August 16 J. A. was discharged in fairly good physical condition. The infant had recovered from his pulmonary infection and had gained 1,600 Gm. since his admission to the hospital.

The baby did well at home for about three weeks. Then the coughing and a nasal discharge reappeared and became progressively worse until the child was admitted to the hospital for the third time nine days later, September 23. The patient appeared to be in extremely poor condition: Emaciation was extreme; coughing was frequent, and numerous moist rales could be heard on auscultation of the lungs. A roentgenogram of the chest revealed exaggerated bronchovascular markings, and many patches of increased density in the medial zones of the lungs were interpreted as chronic bronchopneumonia. Sulfadiazine therapy was started at the time of admission, as penicillin was not then available. This drug therapy was continued to no avail, and after a sudden change for the worse the child died on December 2. There was no terminal episode of asphyxia, which is frequently found in these cases.

CASE 2.—M. G. (S. 19), a white girl, was seen for the first time at the age of 9 months on June 5, 1943. Three weeks after birth her respirations were somewhat difficult and noisy when she was sleeping, and a diagnosis of laryngeal stridor was made by the attending physician. The stridor persisted without giving rise to too much difficulty until the child was 3 months old, when a cough made its appearance. At first the cough was not troublesome, but as time went by the spells of coughing became more frequent. The infant also failed to gain weight, although her appetite was good. One month prior to admission the paroxysms of coughing became so frequent and severe that she was taken to a hospital in Philadelphia for treatment of laryngeal obstruction; there a diagnosis of cystic fibrosis of the pancreas with pulmonary complications was made because of the discovery of steatorrhea. The baby was transferred to the Babies Hospital for further care and study. The child's condition at this time was so poor that she was moved in an oxygen tent by ambulance.

At no time did the child have diarrhea; but the number of stools had consistently been two or three daily, and their consistency and bulk had been considered normal. However, it had been noted by the mother that the odor of the stools had become more and more foul.

On admission the infant appeared moribund. She was emaciated and extremely dyspneic. The cyanosis became pronounced on her withdrawal from the oxygen tent. Her chest was emphysematous, and throughout both pulmonary fields numerous moist rales could be heard. Showers of fine rales were present over the left anterior hemothorax. A roentgenogram of the chest at this time showed both lungs to be studded with fine shadows of increased density, and there were extensive patches of consolidation. The changes were most pronounced on the left side and were thought to resemble the changes found in disseminated hematogenous pulmonary tuberculosis. Two tuberculin tests (0.001 mg. and 0.01 mg.) elicited negative reactions. Hemolytic Staph. aureus (mannitol fermenting and coagulase positive) and beta hemolytic streptococci were recovered from the nose and throat, the lung (by puncture) and the blood stream. The infecting organisms were shown to be sensitive to penicillin.

The child was placed on a diet for pancreatic deficiency and given sulfadiazine on admission. After five days the administration of sulfadiazine was discontinued, and a week after admission penicillin therapy was begun. The drug was administered by intramuscular injection, and an average of 20,000 units was given daily for fourteen days, with a total of 235,000 units. The improvement on this therapy was dramatic. After three days the child's respirations were much easier, the pathologic conditions observed on physical examination had decreased noticeably, and a roentgenogram of the chest showed a reduction in the size and number of the areas of increased density previously seen. The temperature, previously as high as 103 F. came down to normal, and soon the patient was able to remain out of the oxygen tent. The improvement continued, and the child was discharged on Aug. 5, although a few rales could still be heard and increased bronchovascular markings could be demonstrated. In this two month period of hospitalization the child had gained 800 Gm.

Almost immediately after discharge she came down with a cold, and her cough reappeared. Two weeks later she was readmitted for a second time. Her general condition was not so poor as it had been on the first admission, but she appeared moderately dyspneic, slight cyanosis was evident, the respirations were rapid and wheezing and a frequent, loose, hacking cough was present. Numerous fine, moist rales were audible throughout the pulmonary fields on auscultation. The rales were more noticeable over the bases of both posteriorly. A mild infection of the upper respiratory tract and otitis media were also present. The state of nutrition was good, and there had been a gain in weight of 400 Gm. in the intervening two weeks. A roentgenogram showed the same foci of chronic bronchopneumonia previously mentioned. Sulfadiazine therapy was instituted promptly. No improvement was noted. On the contrary, the thoracic signs and the respiratory distress increased to such an extent that the child had to be placed in an oxygen tent two days after admission. The coughing and dyspnea persisted, and a few days later penicillin therapy was instituted. A dose of 20,000 to 40,000 units was given every twenty-four hours for twenty-two days. A slight improvement was noted following the administration of penicillin, but it was by no means as dramatic as it had been during the first admission. A week later there was a recurrence of coughing and cyanosis. A puncture of the lung, which had been performed before the start of penicillin therapy, revealed two colonies of hemolytic Staph. aureus (mannitol fermenting and coagulase positive). Later these organisms were reported to be resistant to penicillin. This resistance affords an explanation of the difference in response to penicillin therapy during the two courses of treatment with this drug.

Despite the clinical relapse, the patient's general condition continued to improve slowly, and a small gain in weight was noted. The frequent coughing and the rales persisted. The areas of pulmonary infiltration increased in number and size throughout this period of observation. On November 5, after two and one-half months in the hospital, the patient was once more discharged. She seemed to be in good condition except for dyspnea on the slightest exertion.

At home the baby was fairly well until the morning of November 14, when she had a violent attack of coughing followed by cyanosis and wheezing respirations. The mother promptly brought the child to the hospital, where she was immediately placed in an oxygen tent. On this admission, the third, the child appeared to be very cyanotic and extremely ill. The lungs were full of moist rales, and the respiratory distress continued to be severe even after oxygen therapy. The temperature was normal until four days before death, when spiking appeared. The child died on November 22 with extreme respiratory difficulty and cyanosis.

CASE 3.—J. M. (S 25), a 26 month old white girl, was admitted to Babies Hospital for the first time on Dec. 17, 1943, with a history of diarrhea since birth and a cough of two months' duration. The patient had had several foul diarrheal stools daily since birth. In the two weeks prior to admission, there had been an acute exacerbation of the respiratory symptoms, with a great increase of coughing and with the appearance of dyspnea and cyanosis. The child had been born prematurely and weighed 5 pounds, 4 ounces (2,380 Gm.) at birth. The weight at 1 year was 13 pounds, (5,897 Gm.), and her best weight had been 23 pounds (10,430 Gm.) at 2 years of age. At the time of admission the child weighed only 16 pounds 9 ounces (7,513 Gm.).

She was found to be decidedly undernourished and underdeveloped; she appeared to be chronically and severely ill and was in moderate respiratory distress. The lips and nail beds were cyanotic, and when she coughed the cyanosis became generalized. Retraction of the intercostal spaces was noted on inspiration, and rales could be heard on auscultation and were especially numerous over the base of the right lung posteriorly. The distended abdomen was in sharp contrast to the severe state of malnutrition. Flat buttocks were observed, as well as a general atrophy of the muscles. A roentgenogram revealed evidence of chronic bronchopneumonia of both lungs. The noticeable changes in the lower lobe of the right lung raised the question of bronchiectasis or of multiple pulmonary abscesses. A diagnosis of cystic fibrosis of the pancreas was made, and the child was placed in an oxygen tent and started on sulfadiazine and an appropriate diet. Administration of sulfadiazine was continued for three days, after which it was decided to try penicillin therapy. On the third day of hospitalization, just before the administration of penicillin was started, a suction tube was passed into the trachea through a laryngoscope. The trachea was seen to be coated by a thick creamy white exudate which narrowed the subglottic region. Cultures were taken of the small amount of the exudate which could be removed from the suction tube, and these revealed a hemolytic Staph. aureus (mannitol fermenting and coagulase positive).

Following this procedure the child was in a critical condition for a number of days. After this period she rallied little by little, and thirteen days later the penicillin therapy was discontinued. A total of 190,000 units was given, with an average of 15,000 units in twenty-four hours. At the end of this period of therapy the child appeared much better. She was more responsive and had less respiratory distress, although the cough persisted. No changes in the chest were noted on a roentgenogram, but examination of the chest revealed a decrease in physical signs.

After the penicillin therapy was discontinued, the condition of the child became gradually worse. On Feb. 19, 1944, one and one-half months after the first course of therapy, a tracheotomy was performed to facilitate the removal of the thick, tenacious, purulent material from the trachea. Direct cultures of material from the trachea showed on two occasions a hemolytic Staph. aureus sensitive to penicillin. The drug was started again by intramuscular injection and by direct instillation through the tracheotomy tube. One cubic centimeter of isotonic solution of sodium chloride containing 800 Oxford units was instilled every four hours from February 19, to February 31 and the concentration was increased to 1,600 units per cubic centimeter from March 31 to April 11. The intratracheal instillation was unsuccessful because it invariably resulted in a paroxysm of coughing, with consequent immediate expulsion of the instilled solution. A total of 850,000 units was given intramuscularly over a period of fifty-one days. Despite chemotherapy, the patient's condition became progressively worse. The purulent drainage increased to such an extent that suction of material from the tube in the trachea had to be performed every few minutes. The cyanosis and the dyspnea were extreme. In addition to the penicillin, sulfadiazine and even antistaphylococcus rabbit serum were resorted to, with no effect. The penicillin was discontinued on April 11, 1944. On April 21, the child died of asphyxiation.

During the course of the illness, numerous cultures of materials from the nose, throat and trachea were taken, all of which revealed a hemolytic Staph. aureus (mannitol fermenting and coagulase positive). The leukocyte count was consistently elevated, frequently as high as 25,000.

CASE 4.—N. M. (S 30), was admitted to the Babies Hospital at the age of 8 months; the infant had had a dry cough and difficult respirations since birth. When he was 10 days old, a diagnosis of atelectasis was made by the attending physician. The gain in weight was always slow, and the formula had been frequently changed without effect. At the age of 4½ months and again at 6 months the infant was given a course of therapy with sulfadiazine in a vain attempt to control what was then thought to be a chronic cold. The stools were never abnormal. The coughing and dyspnea had been much worse for the two weeks prior to admission, and the baby had vomited with almost every coughing spell.

On admission the patient was found to be an emaciated, underdeveloped white boy in acute respiratory distress, with noticeable retraction of the suprasternal notch and the costal margins. Cyanosis of the lips and the extremities was extreme, and the child's expression was one of fear and apprehension. The chest was barrel shaped, and the percussion note was tympanitic. On auscultation numerous moist rales could be heard all over the pulmonic areas. The abdomen was distended, and its fulness contrasted with the wasting away of the rest of the body. The weight on admission was 5,630 Gm.

A roentgenogram taken on Aug. 2, 1944 revealed changes characteristic of chronic bilateral bronchopneumonia. Both lungs were emphysematous. The child was placed on a diet for pancreatic deficiency. After an elevation of temperature to 102.4 F. on August 7, sulfadiazine was given. The child's condition did not seem to improve, and penicillin was given in addition to the sulfadiazine. The patient received 32,000 units daily for a total of seventeen days. Penicillin was also given by inhalation with the aid of a nasal catheter; this procedure soon had to be abandoned because the baby did not tolerate the repeated passage of the catheter through the nose. A slight improvement was noted at first, both in the state of nutrition and in the respiratory symptoms. On August 28, a few days after the administration of penicillin had been discontinued, a roentgenogram

of the chest revealed an increase in the number of areas of consolidation throughout the medial portions of both pulmonary fields, a condition suggesting atelectasis. On August 31 the patient was discharged unimproved, after a month in the hospital.

As soon as the baby left the hospital, a profuse nasal discharge made its appearance; the temperature rose to 102 F., and the stools became watery. Twenty-four hours after discharge, the child was returned to the hospital, on September 1. The administration of sulfadiazine and the intramuscular administration of penicillin were again resumed. Both types of chemotherapy were discontinued after twelve days because no improvement could be seen; but penicillin was given intramuscularly again two days later in desperation, as the patient appeared to be sinking rapidly. Penicillin by inhalation was attempted for a short time on September 23 and then again on October 11. This procedure was difficult to carry out for mechanical reasons. Again no improvement was noted.

On October 14 the temperature rose to 104.8 F. The child was critically ill, and death seemed imminent. After five more days of spiking temperatures, pronounced cyanosis and extreme dyspnea the baby ceased breathing on October 19. He had received 1,724,000 units of penicillin by intramuscular injection and inhalation over a period of fifty-one days. Sulfadiazine had been administered without interruption throughout the periods after both admissions.

Cultures of material from the nose and throat, taken at various times, consistently showed the presence of hemolytic Staph. aureus (mannitol fermenting and coagulase positive). On Oct. 12, 1944 the staphylococci isolated from a culture of materials from the throat were found to be resistant to penicillin in vitro. After the death of the patient a pure culture of hemolytic Staph. aureus (mannitol fermenting and coagulase positive) was obtained, and the organism was found to be resistant to a concentration of 250 units of penicillin per cubic centimeter. Unfortunately, the organism had not been tested for its sensitivity to the drug before chemotherapy was instituted.

CASE 5.—J. E. (S 36), a white girl, was first admitted at the age of 11 months, on Dec. 5, 1944. She had shown a failure to gain weight regularly and had had large, frothy foul stools since birth. Since the age of 2 months the child had been unusually susceptible to infections of the upper respiratory tract. At the age of 7 months the patient had pneumonia followed by a pulmonary abscess which was successfully treated with penicillin. After this episode the baby was fairly well for several months, and on her first admission to the Babies Hospital the respiratory symptoms were found to be so mild that it was not felt that therapy was indicated. After a series of investigations had been carried out, the diagnosis of cystic fibrosis of the pancreas was established. The infant was placed on a strict diet for pancreatic deficiency and discharged from the hospital.

Ten days later the patient was readmitted because of diarrhea and coughing of five days' duration. On physical examination she appeared moderately ill, had loose stools and a productive cough and was slightly cyanotic. Her physical development and state of nutrition were fair. Auscultation of the lungs revealed the presence of fine crackling rales over the base of the right lung and in the right axilla. Roentgenograms of the chest showed the presence of bilateral bronchopneumonia of moderate degree, with especially pronounced changes over the bases of both lungs.

Penicillin was administered intramuscularly for two periods of five and four days respectively. An average of 160,000 units was given every twenty-four hours. Improvement obtained by this therapy was striking. When the child was discharged three and one-half weeks after admission, the results of a physical examination were normal and the roentgenographic evidence of infection had definitely decreased.

Since that time the patient has done very well. She has gained weight and has developed regularly. However, a slight cough persisted, and in March 1945 the patient was readmitted because of an increase in respiratory symptoms. At this time another course of penicillin therapy was given intramuscularly. She has since done well (November 1945).

CASE 6.—R. H. (S 24), was seen here for the first time on Nov. 4, 1943, with a chief complaint of having had abnormally large and foul-smelling stools since birth. Moreover, he had failed to gain weight regularly, and he had also had a persistent cough since the age of 2 months. In June 1943 a diagnosis of atelectasis of the lower lobe of the right lung was made, and after bronchoscopic drainage the patient was said to have improved considerably.

On physical examination the child was found to be a white boy, 8 months of age, fairly well nourished and only slightly underdeveloped for his age. His happy expression, which was present on this as well as on subsequent admissions, was striking and rather representative of the placid, contented expression of patients with congenital pancreatic deficiency, if they are not too acutely ill, as contrasted with the worried, apprehensive, bedraggled facies and attitude of patients with classic celiac disease. No cyanosis of lips or extremities was present, and there was no clubbing of the fingers or toes. Coughing was frequent, but the respirations were quiet, and no retraction of the intercostal spaces or of the suprasternal notch was noted. No rales could be heard on auscultation of the lungs. A roentgenogram of the chest at this time showed a long strip of increased density in the posterior portion of the middle lobe of the right lung, consistent with the presence of either consolidation or atelectasis.

No form of chemotherapy was given during this first admission, but a series of investigations were carried out, which made it clear that the child was suffering from congenital pancreatic deficiency. The patient was discharged on Dec. 5, 1943, on a suitable diet. He did fairly well at home except for the persistent cough, which was productive of large quantities of purulent material.

This child was readmitted in January and in April 1944 for brief periods because of increased respiratory symptoms. Sulfonamide therapy was given on both occasions without much improvement. Throughout this period the child's state of nutrition was maintained remarkedly well, while the roentgenographic examination continued to show evidence of chronic bronchopneumonia, which gradually spread to both lungs even though the most noticeable changes were still found in the middle lobe of the right lung. In July 1944, during his fourth admission, the patient was given penicillin by inhalation. As can be seen from table 3, during this period of hospitalization, from July to September 1944, and during three subsequent admissions the patient received intensive penicillin therapy either by aerosol nebulization or by a combination of aerosol nebulization and intramuscular injections. The dosages, as can be readily seen, were always adequate, and in some instances the amounts of penicillin given were truly outstanding. For instance, in the five days from March 5, to March 9, inclusive, the child, weighing at that time 9 Kg., received 1,800,000 units of penicillin, or almost 400,000 units a day. A total of 6,500,000 units of the drug was administered between July 1944 and April 1945, but the results have been far from satisfactory. Slight improvement was usually noted in the child immediately after each course of therapy, but this generally lasted for only a few days, and then he would begin to cough as hard as he had before the treatments. Serial roentgenologic examinations of the chest failed to reveal any improvement in the extensive inflammatory changes of the lungs previously mentioned. On the contrary, slight but steady progression

of the pulmonary infection was noted. The white blood cell count was, for the most part, around or above the 20,000 mark. The count responded transitorily, if at all, to the penicillin therapy. Numerous moist rales all over the pulmonary fields were constantly observed during these months. Cultures of material from the nose and throat had consistently revealed the presence of Staph. aureus; the organisms recovered from the various cultures were variable in their biologic characteristics and in their resistance to penicillin, as can be seen from table 4.

In spite of the unsatisfactory response of the infection of the respiratory tract, R. H. has done remarkably well as far as his general condition is concerned. Now at the age of more than 2 years he is still cheerful, and his state of nutrition is good even if his degree of growth and development is not up to the standards expected of his age group. This progress can hardly be attributed to the penicillin therapy, which must be considered to have been a failure in this case.

CASE 7.—M. N. (S 29), a white girl of 4 years and 3 months, was admitted for the first time on July 26, 1944, with a chronic cough which had been increasing for the past eight months. Since birth the child's stools had been "fluffy," rather large and extremely foul. She had been kept on a regular diet and had apparently done well until October 1943, when it was discovered that large amounts of fat were present in the stools, and the diet was changed to one which was free of fat. In January 1944, the patient contracted pneumonia and was treated with sulfadiazine. She never fully recovered from this acute episode, and a chronic cough productive of purulent material set in and became progressively worse. In the two months prior to hospitalization increasing cyanosis and dyspnea were apparent.

At the time of her admission to the hospital the child was found to be fairly well developed but thin. She was acutely ill, with rapid respirations, moderate substernal and jugular retraction and cyanosis of the lips; coughing was almost continuous. The temperature was 101 F. There was a pronounced clubbing of the fingers and toes. On ausculation of the lungs numerous moist rales could be heard throughout both pulmonary fields. The abdomen was slightly distended. A roentgenogram of the chest showed extensive inflammatory change scattered throughout both lungs, and especially heavy bronchovascular markings over the bases of both lungs were thought to indicate bronchiectasis. At this time it was believed that the child was on the verge of death, and the day after admission the administration of penicillin by inhalation was instituted as a last desperate effort. Thirty-two thousand units of penicillin was given every twenty-four hours by the nasal catheter method. A total of 368,000 units was given over a period of thirteen days (8,000 units every six hours).

The response to treatment was most gratifying. There was a decided improvement in the cough, the dyspnea and the cyanosis; the temperature and the leukocyte count dropped to much lower levels (fig. 2). A second course of therapy, lasting eight days, was started a few days later, as there was a recurrence in fever, and again the same desirable response was obtained. A third course of penicillin aerosol, of twelve days' duration, was given at the beginning of September. At this time a decided increase in weight was noted. Serial roentgenograms of the chest showed some improvement, even though extensive, scattered shadows persisted throughout the lungs.

On September 16 the patient was discharged, after having been in the hospital for almost two months. During this interval she had received three courses of penicillin aerosol with a total of 960,000 units of the drug. Improve-

ment during hospitalization had been astounding. The child, who had been in imminent danger of her life when admitted, walked away from the hospital a fairly normal-looking, happy little girl of 4½ years.

One of the interesting features of this child's recovery was the complete disappearance of the clubbing of the fingers and toes, which had been so pronounced when she was first admitted. The most striking improvement in the clubbing of the extremities took place during the first hospital stay, and since then all traces of this deformity have gradually vanished.

The patient has been followed periodically since her discharge in September 1944. On two occasions she had an increase in coughing and was readmitted for treatment in November 1944 and February 1945. During the former admission the child was given two courses of penicillin aerosol. In the last admission she received combined intramuscular and inhalation therapy (table 3). Up to the present (December 1945) the patient has been seen periodically and has been found to be progressively improving. On her last physical examination auscultation of the chest revealed no abnormal sounds. Her weight and measurements were within the limits expected of her age group (fig. 3). She has been leading a normal life, with no restriction of activity.

At numerous times during the course of this patient's admissions to the hospital, materials for culture were taken from the nose and throat. While Staph. aureus was consistently found, there was considerable variability in the type of organism. However, all the organisms isolated were found to be sensitive to penicillin (table 4).

Case 8.—S. P. (S 32), a 15 month old white girl, was first seen on Sept. 9, 1944, with a history of chronic diarrhea with large, foul-smelling stools since birth and of a cough since the age of 3 months. The coughing had been of a dry, hacking, paroxysmal type so similar to whooping cough that when it first appeared a diagnosis of pertussis was made. A few months before her admission the physician made a diagnosis of cystic fibrosis of the pancreas and the patient was placed on an appropriate diet, including pancreatin.

On physical examination the child was found to be in fairly good condition. The state of nutrition was fairly normal, and the development was only slightly below the accepted standards. She did not appear acutely ill, and no cyanosis, clubbing or dyspnea were noted, even though a hacking, dry cough frequently occurred. Muscle tone was good, even though the muscular masses were somewhat wasted and the buttocks were slightly flat. The abdomen was barely prominent. A few scattered moist rales could be heard throughout the chest on auscultation. A roentgenogram disclosed a moderate inflammatory reaction throughout the pulmonary area.

Shortly after admission an attempt was made to administer penicillin aerosol by the nasal catheter method. Mechanical difficulties were encountered in the passage of the catheter because of congenitally small posterior openings of the nares; hence we resorted to the mask method of administering penicillin aerosol, which was well tolerated. As a matter of fact, the difficulties encountered with this patient stimulated experiments with the mask. A total of 839,000 units of penicillin was administered by inhalation in two separate courses over a period of twenty-one days. By the end of the second period of treatment the child was much better. Admittedly it was more difficult to evaluate this child's response to therapy because she was brought to us in fairly good condition. To those who kept the baby under close observation it was evident that a change for the better had taken place. The cough subsided; all pathologic conditions observed on

previous physical examination of the lungs had completely disappeared; the white blood cell count had dropped to normal limits from a high of 20,000 on admission and the child's disposition had also improved. These observations were corroborated by a decrease in the inflammatory changes visible in the lungs by roentgenogram.

The patient was discharged on Oct. 28, 1944 and has not been seen since, as the parents moved to Detroit. Her course has been followed there by Dr. Clement A. Smith, who has given her further courses of penicillin by inhalation. Although some degree of pulmonary infection and cough persists, the child is doing well.

A roentgenogram of the chest taken in January 1945 in Detroit was sent to us and showed entirely normal conditions.

CASE 9.—J. R. (S 6) was admitted on Oct. 1, 1944 at the age of 5 years and 8 months. A diagnosis of cystic fibrosis of the pancreas was made at the age of 1 month on the basis of examinations of stools, which had revealed an increase in the amount of total fat in the dried specimens. The child was placed on an appropriate diet, which included large doses of pancreatin. While the stools remained somewhat abnormal in size and odor, the patient did well on this regimen for several years, gaining weight and developing according to schedule. Dietary restrictions were then relaxed. Between the ages of 3 and 4 the pancreatin was gradually decreased in amount until it was discontinued entirely in 1943. This was made necessary by the fact that J. R's mother became sensitized to pancreatin and was subjected to attacks of asthma each time she handled it. This is the second case of sensitization to the medication which we have encountered in the mother of a patient.

The fact that the growth and development of this patient began to fail after the pancreatin was discontinued underscores the importance of this drug in the treatment of patients with congenital pancreatic deficiency. The gradual decline in the child's condition culminated in the appearance of the chronic progressive purulent bronchitis, which is the ultimate outcome of a prolonged dietary disturbance in these patients. In June 1944 a cough set in following an acute infection of the upper respiratory tract. The cough became progressively worse until it was felt in October 1944 that admission to the hospital was imperative for a reevaluation of the patient's condition and for treatment.

Physical examination revealed that this child was only slightly undernourished and was well developed. A dry, hacking cough was frequently heard during the examination, and during the attacks of coughing the lips and extremities became somewhat cyanotic. Slight clubbing of the fingers and toes was present. The abdomen was moderately prominent. On ausculation of the lungs, a few scattered moist rales could be heard. A roentgenogram of the thorax revealed the presence of extensive, generalized, bilateral inflammatory changes with heavy shadows at the bases raising the question of bronchiectasis.

Two courses of penicillin aerosol therapy were given to this patient, totaling 1,000,000 units over a period of twenty-two days. On Oct. 31, 1944 the patient was discharged, after it was felt that considerable improvement had taken place.

Six weeks later the child was seen again. At this time the truly remarkable effects of the penicillin therapy could be evaluated. Since discharge the girl, who had been kept on a diet for pancreatic deficiency, had gained 3 pounds (1.3 Kg.) in weight; the cough had completely disappeared. Roentgenographic examination revealed a decided improvement in the inflammatory conditions which had previously extended throughout the lungs. Improvement was especially noticeable in the lower lobe of the right lung; the heavy shadows suggesting bronchiectasis

had completely disappeared, leaving an almost normal-appearing parenchyma. Since this visit, in December 1944, the child has been doing so well that further treatment has been unnecessary.

CASE 10.—J. H. (S 34) was admitted on Nov. 6, 1944, at the age of 6 years. She had a history of diarrhea and of bulky, fatty stools since early in life. Her growth and development were delayed. When she was 21 months old, a physician made a diagnosis of celiac disease and placed the child on a diet for patients with celiac disease, which included large amounts of vitamins and pancreatic extracts. The patient did fairly well on this regimen, but because of a persistence of her diarrhea and because of the retardation in growth previously mentioned she was admitted to a hospital in New York city in October 1943, at the age of about 5 years. Numerous investigations were carried out, and the conclusion was reached that the child did not have celiac or pancreatic disease but had a congenital megacolon. The diet was modified accordingly and liberalized to include all the foods of a regular diet. The pancreatic extracts were discontinued.

In the ten month interval between January 1944, when she was discharged from this hospital, and November 1944, when she was admitted to Babies Hospital, the child remained on a regular diet. The stools remained abnormal. There was practically no gain in weight, and at some time during the course of 1944 a productive cough made its appearance and persisted.

At the time of her admission to Babies' Hospital the patient was found to be a moderately undernourished, underdeveloped white girl, 6 years of age, who was not acutely ill. There was no respiratory distress. The slightly flat buttocks, the moderate malnutrition, which was more noticeable on the body than on the face, and the slightly prominent abdomen all fitted into the clinical picture of the celiac syndrome. Auscultation of the chest failed to reveal any abnormal changes. However, roentgenologic examination of the chest revealed the presence of mild but diffuse chronic inflammatory changes in both lungs.

A duodenal drainage and other laboratory investigations soon revealed the true nature of the patient's difficulties, and dietary therapy was instituted. The pathologic changes in the lung seemed an indication for penicillin aerosol therapy. A total of 300,000 units of penicillin was given by inhalation over a period of four days during this period of hospitalization. It was difficult to tell at the time whether any improvement had followed the treatment, as the child was in fairly good condition at the time of admission. Another course of therapy was planned, but the child contracted chickenpox and had to be sent home. She was readmitted in January 1945 and then again in February 1945 and received a total of 2,142,000 units of penicillin aerosol in three separate courses. The treatments were given more on a prophylactic basis than on a curative one. Some increase in coughing was noted following a cold prior to her third admission, in February 1945. At present she is doing fairly well, even though some coughing persists. The lungs appear normal on examination by physical methods, but inflammatory changes persist, as shown by roentgenograms.

Cultures of material from the nasopharynx have consistently shown a hemolytic Staph. aureus (mannitol fermenting and coagulase positive) up to March 1945. Two cultures since have shown the presence of Hemophilus influenzae type a.

CASE 11.—M. G. (S 27) was first seen at Babies Hospital on June 11, 1944 at the age of 2½ years. The chief complaints on admission were three to six moderately loose, foul-smelling stools each day for about two years and a cough

since the age of 6 months. The cough had become progressively more frequent and severer, and in recent months it had been commonly followed by vomiting. A failure to gain weight normally and to grow properly had also been noted.

The physical examination on admission revealed an extremely undernourished and underdeveloped child, who was both acutely and chronically ill. She appeared much younger than her 2½ years. In distinct contrast to the good-natured disposition of most patients with congenital pancreatic deficiency, M. G. was irritable and cried bitterly almost without pause. The persistent crying and the almost incessant coughing made the task of physical examination a difficult one. The muscular masses of the patient's extremities were wasted; the buttocks were flat; the ribs were prominent under a skin hanging loosely over them, and the abdomen was moderately prominent and distended. The respirations were rapid and the lips cyanotic. Clubbing of the fingers and toes was noted. Some retraction at the suprasternal notch and in the intercostal spaces could be observed. On auscultation numerous scattered moist rales could be heard throughout the pulmonary fields. A roentgenogram of the chest showed generalized inflammatory changes in both lungs of the type usually found in chronic bronchopneumonia.

During her first hospitalization from June 11 to June 28, 1944 no penicillin therapy was given, but a thorough study was made in order to ascertain the diagnosis. However, sulfadiazine was administered for seven days during this stay.

In November, five months after discharge, the child was readmitted for a course of penicillin aerosol therapy. While at home she had received dietary therapy without alteration of her status. The physical conditions were similar to those of the first admission. The pathologic changes in the lungs had become somewhat worse and were especially noticeable over the lower lobe of the right lung. It was felt by the roentgenologist that bronchiectasis or multiple pulmonary abscesses could not be ruled out. Cultures of material from the nose and throat were repeatedly positive on this as on previous and subsequent admissions for hemolytic Staph. aureus (mannitol fermenting and coagulase positive). At this time treatment consisted of two courses of penicillin administered by the inhalation method. The first course of penicillin lasted for six days, and a total of 435,000 units was given. During the second course 795,000 units was given over a period of five days (table 3). The patient responded dramatically to this therapy, and as a result her clinical status was vastly improved within a few days. The emotional state of the child was quite different; the appetite improved; the coughing decreased but never completely disappeared, and there was a gain in weight of 900 Gm. After these two periods of treatment the physical pathologic changes in the lungs decreased progressively and eventually disappeared. At the time of the second discharge from the hospital the lungs were entirely clear on auscultation and percussion, and no rales could be heard. The improvement in the lungs as shown by roentgenogram was slight.

On Dec. 13, 1944 M. G. was sent home again much improved. Up to the present this patient has been admitted twice for penicillin therapy during the period from Jan. 26 to Feb. 19, 1945. Each of these admissions was prompted by an exacerbation of the respiratory symptoms. Nevertheless, the child has been remarkably well since the first course of penicillin aerosol, given in November 1944. The infection of the respiratory tract has certainly not been cured; but at no time during the past eight months has the child slipped back to the pitiful physical state in which she first came to us.

The mode of administering penicillin has been somewhat different during the last two admissions. The doses have been increased, and on almost all occasions

the drug has been administered concurrently by intramuscular injection and by inhalation. These changes in administering the drug did not result in an increased response to therapy on the part of the patient as compared with the response to the original administration of penicillin, by aerosol nebulization only. It is interesting to note (table 4) that the Staph. aureus isolated from the nose and throat remained consistently sensitive to penicillin.

CASE 12.—E. D. (S 38), a white girl of 2 years and 9 months, was admitted on Dec. 13, 1944 with the chief complaint of bronchitis of two months' duration. The stools had been loose and bulky since birth, and the patient had failed to gain weight and to develop as expected. On the basis of the past history and of the appearance of the stools, a diagnosis of celiac disease had been made by a physician in August 1944, and a diet for patients with celiac disease had been started at that time. In October the child caught a severe cold, and since that time a productive cough has existed. Ten days prior to admission here the child was hospitalized in another hospital because a fever had developed, and the cough had become severe. A leukocyte count of 32,000 was found at this time. On Dec. 12, the patient was transferred to Babies' Hospital for study.

On physical examination the patient was found to be undernourished and undersized. She was pale and slightly cyanotic and looked chronically ill. The respirations were rapid and moderately labored; there was slight clubbing of the fingers and toes. The abdomen was mildly distended, and both lungs were filled with coarse, moist rales. A roentgenographic examination suggested chronic bronchopneumonia. The inflammatory changes were bilateral but were more noticeable in the base of the left lung.

During the first admission the child was in the hospital from Dec. 13, 1944 to Feb. 14, 1945. Three courses of penicillin aerosol were given and one of combined inhalation and intramuscular therapy (table 3). A total of 2,830,000 units of the drug was given over a period of twenty-three days. There was an immediate favorable clinical response to the penicillin aerosol. The child appeared better and gained weight; her appetite improved, and her disposition also changed for the better. She was bedridden on admission, but after the first two courses of therapy she was able to take part in the activities of the ward. She walked about and was able to eat at the table with the other children. The coughing had decreased considerably, and the respiratory difficulty had all but disappeared. The chest became completely normal to physical examination. The darker side of the picture was that the white blood cell count remained persistently elevated, usually over 20,000 per cubic millimeter, and that no change could be found in the serial roentgenograms of the lungs. No further improvement was noted after the two other courses of therapy given during this admission. However, no ground was lost.

She was admitted again in March 1945, at which time two more courses of penicillin by inhalation were administered. On this admission the response was similar to that previously described. What little ground had been lost was quickly regained, but no improvement was noted in the roentgenograms of the chest or in the white blood cell count. The patient was discharged on March 23 and was again readmitted on April 19, with an increase of respiratory symptoms. She received penicillin parenterally for two weeks and by aerosol nebulization during the remainder of her ten weeks' stay. Sulfadiazine was given concurrently after the fourth week. Her response was poor, and she was allowed to go home for a rest period on July 1. She returned two weeks later with some increase in cough and with orthopnea. Penicillin therapy by both intramuscular and inhala-

tion routes was resumed without benefit, and she died on July 28. At postmortem examination the trachea and the bronchial tubes were seen to be filled with a thick mucopurulent material. The diagnosis of cystic fibrosis of the pancreas was confirmed.

CASE 13.—G. W. (S 41), a 4 year old white boy, was admitted on March 8, 1945. The chief complaint was a chronic cough of nine months' duration. The stools were described as foul and large since birth. Growth and development had proceeded normally, and the child's general condition had been good until August 1944. At this time a cough was noted, and it persisted despite all attempts at medical treatment. In January 1944, after a cold and otitis media the respiratory symptoms increased, and thereafter the patient's condition steadily declined.

At the time of admission the patient was found to be fairly well developed for his age but badly undernourished. He was severely ill, dyspneic and orthopneic, with suprasternal, xiphoid and intercostal retractions. When the lungs were auscultated, numerous scattered rales could be heard all through the pulmonary fields. Some wasting of the muscular masses, flatness of the buttocks and prominence of the abdomen were also noted. Roentgenograms of the lungs revealed the presence of large and small patches of increased density consistent with an extensive bilateral bronchopneumonia.

It was evident that the child was in a critical condition. Therefore, penicillin aerosol and a suitable diet were instituted immediately. Diagnostic studies carried out later, when the patient had improved, confirmed the diagnosis of cystic fibrosis of the pancreas. Penicillin by inhalation was given, the first time for one week, and the improvement was striking. As soon as forty-eight hours after the treatments were started, the child became much more comfortable and happy and was allowed to sit up in an armchair instead of lying in bed propped up by pillows. Another course of penicillin aerosol of eleven days' duration was begun a few days later. Between these two periods of inhalation therapy penicillin was given by mouth in relatively small doses—175,000 units in twenty-four hours for three and one-half days. The total amount of penicillin absorbed from the intestinal tract was probably so small that it can be disregarded from a therapeutic standpoint.

By the end of the first hospitalization period this boy was walking about the ward and playing with the other children. The roentgenologic signs of the extensive bilateral bronchopneumonia disappeared, leaving as residual changes only slight thickenings of the bronchovascular markings in the bases.

Since discharge the child has been readmitted for another course of penicillin aerosol. At the present time he is in good physical condition, and he is able to take part in the activities of children his age. Some coughing is still present, and scattered inflammatory changes are again visible in the lungs by roentgenogram.

CASE 14.—P. D. (S 44) had been coughing intermittently for almost two years before her first admission to Babies Hospital, at the age of 4 years and 1 month. Her father and sister suffer from asthma. An older sibling died in infancy of pancreatic fibrosis. At 6 months of age the child began to have two to three loose, foul stools daily but was well otherwise and gained weight regularly. At 2 years of age she had bronchopneumonia after which chronic cough developed. The respiratory symptoms became progressively worse, and her general condition began to fail. In September 1944, the patient was admitted to the Children's Hospital in Buffalo, where a diagnosis of cystic fibrosis of the pancreas was made and penicillin was given intramuscularly. The child responded to treatment and

was better for some weeks, after which the pulmonary infection began to progress again. A restricted diet had been given ever since the diagnosis was established.

On her admission to the Babies Hospital the child was undernourished, underdeveloped, extremely irritable and acutely ill. From time to time exhausting paroxysms of coughing occurred, and the patient became decidedly cyanotic and listless. Retraction of the sternum was present, and numerous moist rales were heard over both lungs. The loss of muscular masses and the distention of the abdomen were noticeable. Clubbing of fingers and toes was pronounced. Roentgenograms of the chest showed extensive inflammatory changes in both lungs.

Administration of penicillin was started immediately both by aerosol nebulization and by continuous intramuscular drip. A total of 360,000 units was administered every twenty-four hours for twelve days by the two methods combined. Another course of penicillin, this time only by inhalation, was given after a rest period of about a week. The immediate improvement was striking, and the child was discharged five weeks after admission, considerably improved. This improvement has continued since her discharge, and the patient is now a chubby, happy, normal-appearing youngster. She has gained 10 pounds (4.5 Kg.) in weight in six months and now weighs 31 pounds (14.1 Kg.). Her fingers show no vestige of clubbing. She has had mild asthma on occasion but no longer coughs.

Case 15.—A. G. (S 43), was admitted to the hospital at the age of 6 months on April 3, 1945. Foul, frothy, large stools had been noted since birth, and the gain in weight had always been poor. At the age of 2½ months he had been admitted to the Greenwich Hospital in Connecticut because of bronchopneumonia. Sulfonamide therapy and various formulas were tried to no avail, and after a stay of three months he was transferred in essentially the same condition to Babies Hospital. At the time of admission the patient was found to be emaciated and acutely ill, with extreme respiratory distress. Cyanosis was pronounced and suprasternal and intercostal retractions were present. There were moist rales over both pulmonary fields on auscultation. The baby was immediately placed in an oxygen tent and given a diet for pancreatic deficiency and treatment with penicillin. The drug was given first by intramuscular injection alone and then by means of aerosol nebulization and intramuscular drip combined for a period of twenty-five days. A considerable amount of mechanical difficulty was encountered in administering penicillin by inhalation to this child as to other children of less than 1 year of age. Some improvement was noted after therapy, with a slight gain in weight and a decrease in the respiratory distress, which enabled the patient to remain out of the oxygen tent without too much discomfort. After about two weeks the symptoms reappeared, and the administration of penicillin was started again, this time only intramuscularly. The drug was administered for thirty-seven days and again a slight improvement was noted after the therapy. This period of respite did not last long, however, and the pulmonary infection progressed during therapy. On July 20, 1945 the patient died. A total of 13,100,000 units of penicillin had been given intramuscularly and by aerosol nebulization.

Mrs. M. O. Lipman aided us by carrying out some of the titrations of the sensitivity to penicillin of strains of hemolytic Staphylococcus aureus.

CELIAC SYNDROME

V. Genetics of Cystic Fibrosis of the Pancreas With a Consideration of Etiology

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THE etiology of cystic fibrosis of the pancreas is an unsolved problem. It is not only an interesting puzzle in the abstract but a matter of practical importance, since any hope which there may be of decreasing the incidence of the disease depends on an understanding of its cause. Suggestions as to the causation have included the following: It may be a hereditary disease;[1] it may be the result of a dietary deficiency during pregnancy or early infancy[1b]; it may be the result of intrauterine infection[2] or of infection during early infancy. The more immediate mechanism of the production of the changes in the pancreas has also been attributed to obstruction of the large or small ducts[1b] or to some abnormality of the secretion of the acinar cells,[3] with an abnormal viscosity of their products.[4] There is general agreement as to one attribute of the disease, its occasional presence in several children of the same parents. This observation suggests that the disease may be hereditary, but it is also compatible with the hypothesis of intrauterine infection or of dietary deficiency during pregnancy. The methods

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From the Department of Pathology and Pediatrics, Columbia University College of Physicians and Surgeons, and the Babies Hospital.

1. (*a*) Garrod, A. F., and Hurtley, W. H.: Congenital Family Steatorrhea, Quart. J. Med. **6**:242-258 (Jan.) 1913. (*b*) Andersen, D. H.: Cystic Fibrosis of the Pancreas and Its Relation to Celiac Disease: A Clinical and Pathologic Study, Am. J. Dis. Child. **56**:344-399 (Aug.) 1938. (*c*) Flax, L. J.; Barnes, M., and Reichert, J. L.: Vitamin A Absorption and Its Relation to Intestinal Motility in Fibrocystic Disease of the Pancreas, J. Pediat. **21**:475-484 (Oct.) 1942. (*d*) Howard, P. J.: Familial Character of Fibrocystic Disease of the Pancreas, Am. J. Dis. Child. **68**:330-332 (Nov.) 1944.

2. Brody, H.: Concerning the Etiology of Cystic Fibrosis of the Pancreas, abstracted, New York State J. Med. **41**:1256-1259 (June 15) 1941.

3. Blackfan, K. D., and Wolbach, S. B.: Vitamin A Deficiency in Infants: A Clinical and Pathological Study, J. Pediat. **3**:679-706 (Nov.) 1933.

4. Farber, S.: (*a*) The Relation of Pancreatic Achylia to Meconium Ileus, J. Pediat. **24**:387-392 (April) 1944; (*b*) Pancreatic Function and Disease in Early Life: V. Pathologic Changes Associated with Pancreatic Insufficiency in Early Life, Arch. Path. **37**:238-250 (April) 1944.

of the geneticist offer a means of determining whether or not a disease is hereditary and, if so, in what manner it is transmitted. The present contribution represents an application of these methods to a group of cases investigated at the Babies Hospital and to data obtained from case reports in the literature, with an evaluation of the evidence as to the nature of the disease process.

EXPERIMENTAL OBSERVATIONS

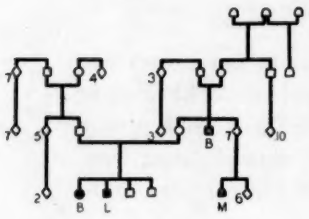
1. *Collection of Data.*—The data consist of two types of observations. One of these is a careful record of the fate of all siblings of infants with proved pancreatic fibrosis seen in the Babies Hospital between January 1938 and May 1945. All siblings under the age of 4 years were checked for steatorrhea by means of microscopic examination of the feces. Forty-seven families were included in the series.

The second set of observations consists of a detailed record of all relatives as known to the parents, with especial respect to death in infancy and childhood, in twenty of these families. The selection of families to be thus investigated was based on two requirements: proof of the disease in one child of the family and cooperation of the parents. The cases were not selected on the basis of high incidence among siblings or more distant relatives, and data on all families which were investigated are included. Proof of the disease was based either on postmortem microscopic examination of the pancreas or on clinical evidence consisting of a characteristic course, demonstration that trypsin was absent from the duodenal juice and that steatorrhea was present when the patient was on a normal diet, including whole milk.

The sources of the information were the parents and sometimes also the grandparents of the patient. In many cases the parents extended the investigation by correspondence with more distant relatives; it was rarely possible to obtain first hand information from the latter, since the people concerned usually lived at a distance, in another state or often on another continent. The data are therefore limited to partial information about three generations in most cases.

Another and more severe limitation is the fact that the disease has been recognized for only a few years and is still unfamiliar to many physicians; hence it is not surprising to find no cases of proved fibrocystic disease of the pancreas among relatives more distant than siblings. Cases of death in infancy or childhood following an illness resembling one of the manifestations of fibrocystic disease are considered "probable." For the sake of clarity and uniformity the cases of probable disease are defined as cases which fit one of the following descriptions: (*a*) death in the neonatal period from congenital intestinal obstruction; (*b*) death from bronchopneumonia in the first year of life of a previously "sickly" infant or of one who has failed to gain without known adequate cause or has had chronic diarrhea; (*c*) death in childhood between the ages of 1 and 12 years from pneumonia following either chronic cough and retardation of growth and development or known chronic diarrhea; (*d*) death in infancy of the majority of a family of 6 or more siblings, and death from pneumonia in infancy or childhood, details unknown. These symbols are used in the accompanying chart. *M* and *S* refer to miscarriages and stillbirths and are recorded, since the frequent occurrence of miscarriage in 10 siblings of infants with proved fibrocystic disease of the pancreas led to the thought that there may be a group of cases of the same basic disease in which some as yet unrecognized associated anomaly is lethal during fetal life.

CASE 3



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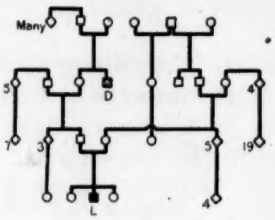

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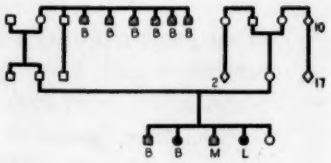

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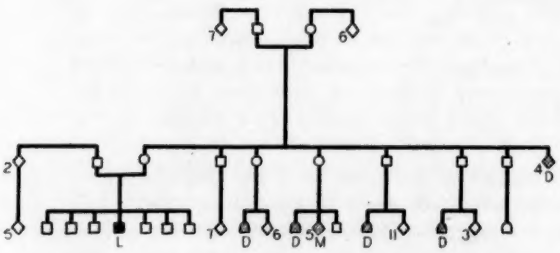

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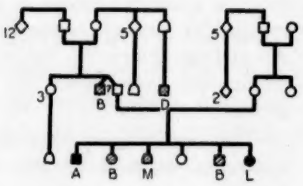

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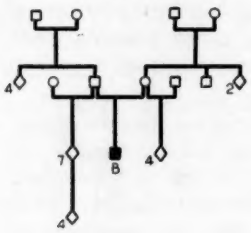

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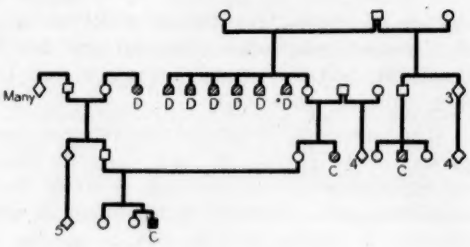

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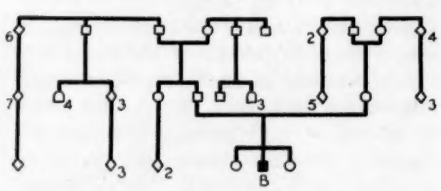

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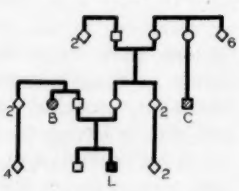

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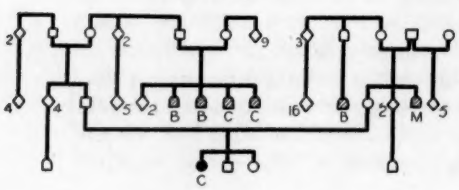
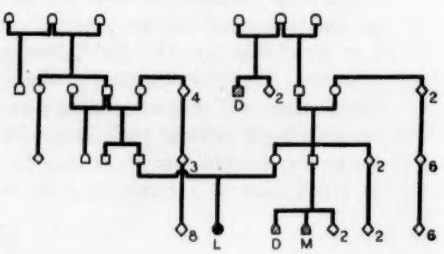
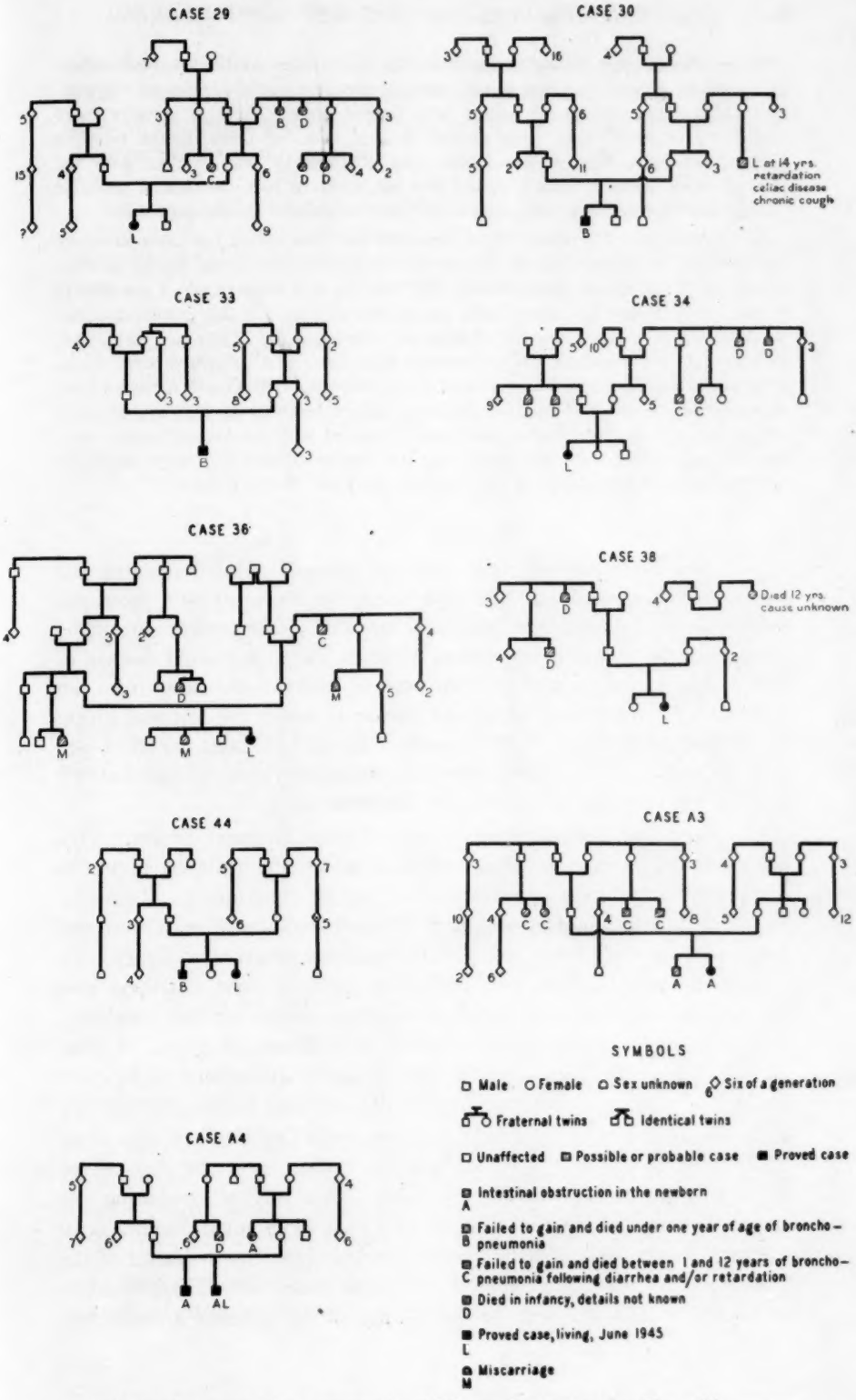


CASE 27





Incidence of congenital pancreatic deficiency in twenty families with one or more proved cases.

This unsubstantiated theory is mentioned as a stimulus to further observation. It should be pointed out that in the cases of probable cystic fibrosis of the pancreas among the siblings of infants with proved disease there is actually more probability of the disease being present than in cases of more distant relatives because the description of the disease was obtained by one familiar with the various manifestations, from a parent who has observed both the case of probable disease and the one of proved disease and is in a position to compare them.

2. *Cases in the Literature.*—The literature has been culled for cases in which the presence or absence of the disease in other members of the family is mentioned. It is not always clear whether the mention of a second case of the disease in the family means that there were no normal siblings. In the present analysis the assumption is made that all siblings are accounted for if any are mentioned, and the data are therefore less trustworthy than those first presented here. Cases in which the patient was the only child or in which no siblings are recorded have been omitted. The cases reported from the Babies Hospital in 1938 are included among those from the literature and are not classed with the present series, since the family records were abstracted from the hospital charts and were originally obtained without knowledge of the familial character of the disease.

ANALYSIS OF DATA

1. *Sex Incidence.*—If only cases of proved cystic fibrosis of the pancreas be included and the data from the literature and from the present series be considered together, one half of the patients are male. Analyzing these data as to source, 32 of 51 cases of proved disease of the present series, or 62.7 per cent, are of boys; of the cases from the literature, 24 of 60 cases of proved disease in which the sex was given, or 40 per cent, are of boys; together 56 of 111 cases, or 50.4 per cent, are of boys. The higher incidence among girls recorded previously[1b] is therefore probably the result of a sampling error.

2. *Incidence Among Siblings.*—A. Babies Hospital Series: This comprises forty-seven families, with a total of 105 children in whom the presence or absence of the disease can be determined. Ten miscarriages and 2 infants dying in very early infancy of an illness not suggestive of fibrocystic disease are excluded from this figure. In sixteen of these families the patient was the only child. If these also be excluded as contributing no information as to familial incidence, there are thirty-one families comprising 89 children, of whom 35 were proved to have the disease and 9 more probably did, a total of 44 cases (table 1). This gives an incidence of 49.4 per cent in affected families, a figure undoubtedly far too high, since many families had only 2 or 3 children, and by our criteria 1 of these must have the disease for the family to be included in the series. One way of combating the statistical error inherent in dealing with data from small families is to subtract 1 case from each family and to determine the incidence of the disease in the remaining siblings. On this basis (44—31)/(89—31), or 13/58, or 22.4 per cent, of the siblings of the patients are affected.

This figure is close to the 25 per cent expected in mendelian recessive traits. It has a practical application in giving information to parents of an infant with a proved disease as to the probabilities that subsequent children will have the disease.

TABLE 1.—*Incidence of Fibrocystic Disease Among Siblings (Babies Hospital, January 1938—May 1945)*

Case	Proved	Probable	Normal	Other
1	M1	....	....	....
2	F3	F2	M1	....
3, 22	M1, F2	....	M3, M4	....
4	M2	....	F1	....
5	M3	....	M1, M2	....
6	F2, F4	M1	F5	U3, Mis.
7	M4	....	F1, M2, F3	....
8	M1	....	M2	....
9	M1	....	....	....
10	F3	....	U1	U2, died of jaundice at 1 week
11	M4	....	M1, M2, M3, M5, M6, M7	....
12	M2	....	F1	....
13	M1A, F6	F2, M5	F4	U3, Mis.
14	M1	....	....	11 half-sibs.
15	M2	....	U1	....
16	M2	....	F1, F3 (twin to 2)	....
17	M1	....	....	....
18	M1	....	....	....
19	F2	....	F1, M3	....
20	M2	....	F1, F3	....
21	M2	....	M1	....
23	M1	....	M2	....
24	M3	M1A	F2	....
25	F1	....	M2, F3	....
26	M2	....	M1	....
27	F1	....	....	....
28	F1	....	....	....
29	F1	....	M2	....
30	M1	....	M2	....
31	M2	....	F1	....
32	F3	F1A, M2	....	....
33	M1	....	....	....
34	F1	....	F2, M3	....
35	M1	....	....	....
36	F4	....	M1, M3	U2, spina bifida
37	F1	....	....	....
38	F1	....	F2	....
39	M4	....	....	....
40	M1	....	....	U1, 2, 3, Mis.
41	M3	....	M2, M4	U1, Mis.
42	M3	M2	F1	....
43	M1	....	....	....
44	M1, F3	....	F2	....
A1	F1A	....	....	....
A2	F1A	....	....	....
A3	M2A	M1A	....	....
A4	M1A	....	....	....

M = male; F = female; U = sex unknown. The number gives the rank order in a sibship. A = congenital intestinal obstruction; Mis. = miscarriage.

A second method of analysis is the calculation of the expected number of instances of a recessive trait in a series of families of the size distribution of those of the present series and the comparison of this figure with the observed incidence.[5] This computation gives the figure

5. Hogben, L.: The Analysis of Pedigrees, in Blacker, C. P.: The Chances of Morbid Inheritance, Baltimore, William Wood & Company, 1934, pp. 405-427.

of 55.8 expected instances, which approximates the observed number of 60 cases of proved and probable fibrocystic disease of the pancreas.

B. Case Reports in the Literature: Similar calculations of the incidence of the disease among siblings, based on case reports in the literature, are recorded in table 2.[6] Fifty-six families have been found in which there were 1 or more cases of proved fibrocystic disease of the pancreas, and in which the presence or absence of the disease in siblings was recorded. These families comprise a total of 177 children, of whom 67 were proved to have the disease, 27 probably had it and 83 gave no evidence of it. Fifty-three and one-tenth per cent of the total number of siblings and 31.4 per cent of siblings after subtraction of 1 case from each family had or probably had the disease. This incidence is higher than among the Babies Hospital series, probably because of the tendency of authors to report abnormal conditions more frequently than normal ones. The expected number of cases in families of this size is 75.11, against the observed figure of 94. Further inspection of the figures shows that this discrepancy is chiefly due to an excess of observed cases in families in which 2 children are recorded, both of whom had the disease; it is reasonable to assume that unrecorded normal children were present in some of these families. Calculations based on a study of twenty-six families comprising 3 or more children give an expected figure of 40.8 and an observed one of 45.

Taking the two series together, there are a total of sixteen families in which 2 siblings were proved to have the disease and twenty-four

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6. (*a*) Kramer, B., in discussion on Andersen.[1b] (*b*) Cited by Andersen.[1b] (*c*) Blackfan, K. D., and May, C. D.: Inspissation of Secretion, Dilatation of the Ducts and Acini, Atrophy and Fibrosis of the Pancreas in Infants: A Clinical Note, J. Pediat. **13**:627-634 (Nov.) 1938. (*d*) Rauch, S.; Litvak, A. M., and Steiner, M.: Congenital Familial Steatorrhea with Fibromatosis of the Pancreas and Bronchiolectasis, ibid. **14**:462-490 (April) 1939. (*e*) Harper, M. H.: Congenital Steatorrhea Due to Pancreatic Defect, Arch. Dis. Childhood **13**:45-56 (March) 1938. (*f*) Jeffrey, F. W.: Cystic Fibrosis of the Pancreas, Canad. M. A. J. **45**:224-229 (Sept.) 1941. (*g*) Deem, H., and McGeorge, M.: Steatorrhea in Infancy, New Zealand M. J. **40**:155-164 (June) 1941. (*h*) Rasor, R., and Stevenson, C.: Cystic Fibrosis of the Pancreas: Case History, Rocky Mountain M. J. **38**:218-220 (March) 1941. (*i*) Attwood, C. J., and Sargent, W. H.: Cystic Fibrosis of the Pancreas with Observations on the Roentgen Appearance of the Associated Pulmonary Lesions, Radiology **39**:417-425 (Oct.) 1942. (*j*) Daniel, W. A., Jr.: Fibrocystic Disease of the Pancreas: Report of Eight Cases, Am. J. Dis. Child. **64**:33-42 (July) 1942. (*k*) Kennedy, R. L. J., and Baggenstoss, A. H.: Fibrocystic Disease of the Pancreas, Proc. Staff Meet., Mayo Clin. **18**:487-493 (Dec. 15) 1943. (*l*) Philipsborn, H. F., Jr.; Lawrence, G., and Lewis, K. C.: The Diagnosis of Fibrocystic Disease of the Pancreas Based upon Twenty-Six Proved Cases, J. Pediat. **25**:284-298 (Oct.) 1944. (*m*) Kohlbry, C. O., and Wells, A. H.: Congenital Fibrocystic Disease of Pancreas, Minnesota Med. **27**:289-290 (April) 1944. (*n*) Andersen.[1b] (*o*) Flax, Barnes and Reichert.[1c] (*p*) Howard.[1d] (*q*) Blackfan and Wolbach.[3]

more in which 1 case of fibrocystic disease of the pancreas was proved and 1 or more additional cases were probable, making a total of forty families in which there is evidence of pancreatic fibrosis in 2 or more

TABLE 2.—*Incidence of Fibrocystic Disease Among Siblings; Data from Literature*

Author	Proved	Probable	Normal	Other
Passini, 1919	F, U	....	....	.....
Clark and Hadfield, 1924	F	U, U	U, U, U	2 stillborn
Burghard, 1925	F	....	U, U (twin to F)	.....
Harper, 1930, case 1	F	....	U, U, U, U	.....
Case 2	F	U	....	.....
Higgins and Mallory, 1931	M	U	F	.....
Blackfan and Wolbach, 1933, cases 10 and 13	F, F, twins	....	....	.....
Huet, 1934	M	....	F	.....
Tiling, 1935	F	U	U, U	.....
Fanconi and others, 1936, case 1	F	U	....	.....
Garsche, 1936, case 3	F	....	U, U	.....
Andersen, 1938, case 4	F	....	F	.....
Case 7	F	U	....	.....
Case 9	F	....	U	.....
Case 11	F	....	F, F, F	.....
Case 12	F	U	....	.....
Case 13	M	....	F	.....
Case 14	M	....	U, U, U	.....
Case 20	F	....	U	.....
Case 21	M	....	U	.....
Case 23	M, F	....	....	.....
Case 24	F	....	U, U, U	.....
Case 37	F	....	U, U	.....
Kramer, 1938	F, M	....	....	.....
Blackfan and May, 1938	UA, UA, twins	....	....	.....
Rauch and others, 1938, case 1	F	M	....	.....
Harper, 1938, case 1	F	....	M	.....
Case 3	F	U	U	.....
Case 5	F, M	....	U	.....
Jeffrey, 1941, case 2	MA	....	U, U, U, U, U, U, U	.....
Deem and McGeorge, 1941, case 1	F, MA	....	....	.....
Rasor and Stevenson, 1941	M	....	M, twin	.....
Attwood and Sargent, 1942, case 2	F	UA, twin	F	.....
Case 4	F	....	U	.....
Daniel, 1942, case 1	F	U	U	.....
Case 3	M	....	M, twin	.....
Case 4	F	....	U, U	.....
Case 5	M	U	....	.....
Flax and others, 1942	F, UA	....	....	.....
Kennedy and Baggenstoss, 1943, case 2	U	U, U, U, U, U	U, U, U	.....
Case 4	U	U	....	.....
Cases 5 and 6	M, F	....	....	.....
Phillipsborn and others, 1944	F	....	U, U, U	.....
Case 1	....	....	U, U, U	.....
Case 5	M	....	U, U	.....
Case 7	M	M	....	.....
Case 8	M	U	U, U, U (twin to M)	.....
Case 9	F	....	U, U, U, U	U, died of hepatitis
Case 13	F, U	....	....	.....
Case 14	M	....	U, U	.....
Case 16	M	....	U, U	.....
Case 18	M	U	....	.....
Case 24	M	....	U, U	.....
Case 25	FA	U	....	.....
Howard, 1944	M, F	F	M, M, M	.....
Kohlbry and Wells, 1944	M	....	F	.....

* Symbols as in table 1.

siblings of a total of eighty-seven families with 2 or more siblings. There is little doubt that pancreatic fibrosis may occur in several children of the same family.

In this brief series a case of congenital intestinal obstruction in a family is associated with a high incidence of pancreatic deficiency in

that family. The families providing data for this observation are those of cases 13, 24, 32, A1, A2, A3 and A4 (chart); in these families there are a total of 16 children, of whom 8 had congenital intestinal obstruction and 6 more had or probably had fibrocystic disease of the pancreas, leaving only 2 normal children. Further data are required before this association can be accepted as a consistent and significant one.

The disease may become something of a family scourge. There are 7 families in each of which there is 1 case of proved fibrocystic disease, and in which a total of 3 or more siblings had or probably had the disease:

Author	Number of Proved and Probable Cases	Total number of Siblings
Clark and Hadfield	3	6
Daniel (case 2)	4	11
Kennedy and Baggenstoss (case 2)	6	9
Howard	3	6
Present series (case 6)	3	4
(case 13)	4	5
(case 32)	3	3

3. *Incidence Among Twins.*—There are 8 instances in which fibrocystic disease was shown to be present in 1 or both twins. In 5 of these 1 twin was normal (Burghard,[6b] Rasor and Stevenson,[6h] Daniel,[6j] Philipsborn[6l] and our case 16, chart), in 2 both twins were proved to have the disease,[6c] and in the remaining pair 1 twin had proved and the other probable disease.[6l] In no instance was it clear that the twins were identical; in 2 cases, with 1 normal and 1 affected twin, the sex difference indicated that the twins were fraternal. The fact that 1 twin may be normal while the other has congenital pancreatic deficiency is strong but not conclusive evidence against intrauterine infection or dietary deficiency during pregnancy as the cause of the disease. The occurrence in both twins of some families and in only one of others is compatible with a hereditary causation.

4. *Consanguinity of Parents.*—There is no known instance of consanguinity of the parents of an infant with proved fibrocystic disease of the pancreas. In the family reported on by Garrod and Hurtley,[1a] in which the diagnosis was based on the clinical picture and analysis of feces, the parents were first cousins.

5. *Incidence of Congenital Intestinal Obstruction in Siblings of Infants with Proved Disease.*—The lesion found in the pancreas in some cases of congenital intestinal obstruction, especially in those with meconium ileus, is indistinguishable from that found in the pancreas in cases in which death follows malnutrition and is due to purulent bronchitis with Staphylococcus aureus as the chief organism. Because of the similarity of the pancreatic lesion, it was assumed that the two diseases were related. Support for this assumption is the occurrence of the two disease pictures in siblings in at least 5 instances,[7] and

7. Flax, Barnes and Reichert.[1c] Deem and McGeorge.[6g] Attwood and Sargent.[6l] Philipsborn, Lawrence and Lewis.[6l]

our case 13 (chart). Intestinal obstruction in twins, both with proved cystic fibrosis of the pancreas, was recorded by Blackfan and May.[6c] In the present series a patient with proved pancreatic fibrosis and congenital intestinal obstruction had an older sibling who also died of congenital intestinal obstruction but whose postmortem examination unfortunately did not include examination of the pancreas (case A3). In addition, an older sibling of patient 24 had a congenital intestinal obstruction, with successful surgical intervention; this infant gained slowly; bronchiectasis developed, and it died at the age of 2 years following a bout of coughing. No autopsy was performed. These cases give evidence that congenital intestinal obstruction may occur in 2 siblings and also in siblings of patients who show the somewhat later manifestations of pancreatic deficiency.

6. *Incidence Among Relatives Other Than Siblings.*—It has been pointed out that in few, if any, cases among relatives other than siblings may the presence of the disease be expected to be proved as yet because of the short time during which the disease has been known. A presumptive diagnosis may be made when the description of the illness and death is strongly suggestive. Cases of probable disease among relatives of patients with disease may be grouped as follows:

A. Multiple Deaths in Infancy Among Siblings.

The following examples are recorded:

Author	Children of	Infant Death	Total Siblings
Flax.....	Maternal grandmother	5	6
Howard.....	Paternal great grandmother	7	8
Present series			
Case 6.....	Paternal great grandmother	6-7	8-9
Case 16.....	Maternal great grandmother	6	7
Case 18.....	Maternal grandmother	8	9
Case 25.....	Paternal great uncle	4	6

In two of the above families a little further information is available. In case 6 the paternal grandmother had "6 or 7 brothers and sisters who all died of whooping cough when they were babies." Obviously they could not all have died during the same epidemic, and the cough of the infants with fibrocystic disease of the pancreas is often diagnosed as pertussis. In case 25, 4 of the 6 children of a paternal great uncle died of pneumonia, 2 in the first year of life and 2 in the second.

B. Relatives Having Congenital Intestinal Obstruction: Congenital intestinal obstruction in relatives other than siblings of infants with cases of proved fibrocystic disease of the pancreas has been found only once. This is a case (A4) in which both the patient and a maternal aunt died as a result of this condition.

C. Illness and Death of Infants Other Than Siblings: It has occasionally been possible to obtain a fairly adequate description of the illness and death of infants or children who bear a relation other than sibling to the patient with the proved disease, and the cases are marked

B or *C* on the pedigrees (chart). Exclusive of the families with 3 or more infant deaths there are 15 cases in which 1 or 2 infants in a family failed to gain and subsequently died of pneumonia in infancy or survived the first year but were retarded, had intermittent diarrhea and died of bronchiectasis or bronchopneumonia in childhood. In 2 instances a twin of the father of an infant with a case of proved cystic fibrosis of the pancreas died in infancy, with a history of poor gain and with bronchopneumonia.

The probable instances of the disease in relatives other than siblings of the infants with proved disease are therefore numerous. In spite of lack of proof of the disease in any case, the evidence is cumulative that the disease may appear in several branches of the family tree. Lack of such cases of suggestive disease would cast doubt on the hypothesis that the disease is a hereditary one, in view of its frequency. These data, together with the analysis of the incidence of the disease among siblings, provide support for the hypothesis that cystic fibrosis of the pancreas is the expression of a hereditary factor.

THE ESSENTIAL DEFECT IN FIBROCYSTIC DISEASE

Having ascertained that cystic fibrosis of the pancreas occurs in families in a manner consistent with the behavior of a hereditary trait, it is appropriate to examine the lesions found in the disease in an effort to discover what hereditary trait is thus transmitted and what relationship the lesions bear to each other and to the disease picture. The lesions which have been found most frequently are those of the pancreas, the intestines, the liver and the lungs.

1. *Lesion of the Pancreas.*—Any hypothesis concerning the origin of the lesion in the pancreas will have to take into consideration the following phenomena:

A. The pancreatic lesion is present at birth in most, if not all, cases. It has been demonstrated in the first week of life in many cases of congenital intestinal obstruction due to meconium ileus. Doubts have been expressed as to the presence of the lesion at birth in those cases in which the respiratory symptoms appeared after several months of apparent good health. The fact that the birth weight is usually normal and that the infant appears normal at birth is not evidence against the presence of the lesion, since the exocrine secretion of the pancreas is not concerned in the nutrition of the fetus. The majority of the infants with the disease gain slowly but steadily prior to the appearance of the bronchitis. Proof that the retardation in growth precedes the infection of the respiratory tract is presented for 6 infants whose birth weights and weights at 10 days are known (table 3). Five of these were born in Sloane Hospital and the sixth in another hospital, and

all were later admitted to Babies Hospital because of bronchopneumonia. Proof of the diagnosis is based on microscopic examination of the pancreas in all. Five of the 6 failed by a wide margin to regain their birth weight on the tenth day, and the sixth, who was also the smallest, had just reached birth weight at that time. The mean difference between the two weights was —326 Gm. The infants first began to cough at various ages up to 6 weeks, and all therefore belonged to the "early" group.

Further evidence that the nutritional difficulty begins at birth is found in analysis of the ages at which abnormal stools were first observed. In 19 of 42 cases abnormal stools were noted before the age of 1 month and in 11 more before the age of 6 months; in 8 cases the stools were considered normal for the first six months or longer; in the

TABLE 3.—*Weight at Birth and at the Tenth Day in Infants Proved to Have Cystic Fibrosis of the Pancreas at Postmortem Examination*
Roman Numerals Refer to Cases Reported in 1938; Arabic Numerals to Those Reported in 1945

Case	Birth Weight, Gm.	Minimum Weight		Weight, 10 Days, Gm.	Change, Gm.	Age, First Cough
		Gm.	Day			
XIV	3,650	3,210	5	3,320	—330	4 mo.
XV	3.500	3,030	10	3,030	—470	4 mo.
20	3,220	2,540	4	2,640	—580	3 wk.
30	3,180	.....	..	2,840	—340	1 wk. (?)
VI	2,506	2,212	2	2,268	—238	5 wk.
X	2,352	2,184	3	2,352	0	6 wk.
	Mean				—326	

remaining 4 cases the abnormality was first noted after the infants' admission to the hospital before the age of 10 weeks. Mothers who had previously had normal children were aware of the abnormality before the babies were 6 months old in 22 of 23 cases, while mothers who had previously had no children or only children with the disease failed to observe an abnormality before the sixth month in 7 of 19 cases. The accuracy of the observation is therefore in part dependent on the previous experience of the mother. Moreover, abnormal stools were observed long before the first cough in cases with late onset of infection of the respiratory tract, as defined by the first appearance of the cough after the age of 6 months. In the 16 cases with late onset abnormal stools were observed during the first month in 7, between 1 and 6 months in 5 and after the sixth month in 4. Eight of the 9 mothers who first observed abnormal stools after the infants were 1 month old had not previously had normal children. The balance of evidence is therefore in favor of the thesis that the stools are abnormal from the neonatal period. It appears improbable that the nutritional difficulty originates after birth.

B. The lesion is not a true malformation but manifests itself late in pregnancy. All parts of the pancreas are present; in many cases the main ducts are patent, and in all the islands are normally formed. Acini are present in all patients under 1 year of age and in many older patients. Since the islands of Langerhans bud from the acini during the latter part of the third month of fetal life, it is probable that the development of the pancreas is normal up to that time. Moreover, the lesion is infrequently found in association with true malformations, which take place before the end of the third fetal month. Occlusion of the ducts of Wirsung and Santorini has been demonstrated in some cases, but the inconstancy of this abnormality indicates that it is incidental and probably a sequel to some more basic abnormality. Hurwitt and Arnheim [8] have demonstrated that the pancreatic duct is normally patent from its inception. The occlusion of the duct, therefore, cannot be interpreted as the failure of normal canalization. The hypothesis that the lumen is secondarily obliterated accords with the known facts.

C. Cystic fibrosis of the pancreas has a progressive nature. The lesion varies with the age of the patient. In most reported instances of pancreatic fibrosis associated with meconium ileus, in which death usually occurs in the first week of life, the acini were present in normal numbers and had the normal structure except that the lumens of some were distended with eosinophilic material. The ducts contained similar casts. As age increases, the average size of the cysts also increases, until it is uncertain whether the given cyst originated as a duct or as an acinus. By the age of 1 year many of the acini have atrophied and by the age of 3 or more years the acinar tissue may be entirely replaced by fat, in which there remain a few extremely large cysts and many islands of Langerhans. Since the lesion is evidently in its early phases when recognized in the newborn infants, although well defined, it is probable that still earlier phases of it can be identified. Dr. Beryl Paige has been searching for it in autopsies on fetuses and stillborn infants from Sloane Hospital but has had negative results in a series of 346 consecutive postmortem examinations. In a case of meconium ileus reported by Kaufmann and Chamberlin a lesion was observed which may reasonably be interpreted as an earlier phase of the one commonly found. In this case the acinar cells, though present, appeared irregular and some groups seemed to lack lumens. A few lumens contained eosinophilic material. There was extensive fibrosis within and

8. Hurwitt, E. S., and Arnheim, E. E.: Meconium Ileus Associated with Stenosis of the Pancreatic Ducts: A Clinical, Pathologic and Embryologic Study, Am. J. Dis. Child. **64**:443-454 (Sept.) 1942.

9. Kaufmann, W., and Chamberlin, D. B.: Congenital Atresia of the Pancreatic Duct System as a Cause of Meconium Ileus: Clinical Review of the Literature, with a Report of One Case, Am. J. Dis. Child. **66**:55-67 (July) 1943.

between the lobules. Ducts were few. Islands were normal in appearance. On reviewing our files, we found 5 similar cases, in which death was attributed to congenital volvulus or meconium ileus. These had remained unrecognized because cysts were few or absent, the lumens of the collecting ducts were empty and the fibrosis was moderate in degree. The appearance is compatible with the interpretation that these cases represent an earlier phase of the change than those previously recognized, and further observations should be made.

The evidence just reviewed supports the view first presented by Blackfan and Wohlbach [3] that the fundamental difficulty is the production of an abnormal secretory product by the acinar cells of the pancreas.

2. *Congenital Intestinal Obstruction Associated with Cystic Fibrosis of the Pancreas.*—The lesion most commonly reported is meconium ileus, or obstruction of a patent intestinal lumen by inspissated meconium. The site of the obstruction is usually the ileocecal valve, which is sometimes described as stenosed. The terminal 10 cm. or more of the ileum is not enlarged but contains firm or hard nodules of dry material, which may be gray and free from normal staining with bile. Dilated intestine filled with soft or liquid bile-stained material lies proximal to this and may occupy much of the abdominal cavity. Farber has accumulated evidence that the changes are the result of increased viscosity of the meconium due to lack of pancreatic digestion.[4] This interpretation is more reasonable than that suggested by Landsteiner,[10] that back pressure because of intestinal obstruction forces fecal material into the pancreatic duct and thereby produces inflammation. A confusing feature of the intestinal obstruction is the frequent occurrence of volvulus and the occasional occurrence of peritoneal bands, leading the exploring surgeon to believe that section of the bands or reduction of the volvulus will relieve the obstruction, as in fact it sometimes does. The pathologist who concludes the exploration soon after may likewise be confused. Both phenomena may be interpreted as the result of the intestinal obstruction, which may be expected to result in hypermotility leading to volvulus and to peritoneal irritation resulting in adhesions. Of the 4 cases of congenital intestinal obstruction with cystic fibrosis of the pancreas which are presented, only 1 represents uncomplicated meconium ileus. In 1 of the remainder a peritoneal band bound the ileum to the omentum and was sectioned on the third day. The patient was relieved of obstruction but died of purulent staphylococcic bronchitis on the thirty-first day. In another case a volvulus due to peritoneal bands was reduced and the obstruction relieved; the infant died at

10. Landsteiner, K.: Darmverschluss durch eingedicktes Meconium: Pankreatitis, Centralbl. f. allg. Path. u. path. Anat. **16**:903-909 (Nov. 30) 1905.

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26 days of age of confluent lobular pneumonia. In the fourth case reduction of the volvulus failed to relieve the obstruction, the postmortem diagnosis being stricture of the ileocecal valve with dry impacted fecal material in the terminal ileum. A fifth case, which has been observed quite recently, was considered one of intestinal obstruction due to peritoneal bands and to an abnormal S curve in the ascending colon, both of which received surgical attention without relief of the obstruction. Postmortem examination revealed the characteristic picture of meconium ileus, with inspissated meconium in the terminal portion of the ileum and an underdeveloped and empty colon. It is probable that many cases which are thought to be instances of congenital volvulus are in fact cases of meconium ileus. If pancreatic achylia is present at birth in all cases it must be assumed that the meconium is likewise abnormal, but it rarely produces complete obstruction unless volvulus or peritoneal bands are also present. The alternative view is presented by Farber, that the pancreatic lesion is postnatal in origin in those cases without intestinal obstruction [4a]; this hypothesis ignores the neonatal onset of the nutritional difficulty.

Farber has described eosinophilic concretions in the lumens of intestinal glands in meconium ileus,[4b] and we have been able to confirm this description in several cases. The relationship of these concretions to meconium ileus and to variability in the efficiency of digestion in older patients presents an interesting subject of speculation.

3. *Lesions of the Liver and Biliary Passages.*—It is not uncommon to find local areas of cirrhosis involving regions of 2 to 3 cm. in greatest dimension, usually along the margin of the liver. Histologically these suggest the lesion in the pancreas, for they consist of a concentration of small bile ducts containing eosinophilic concretions and surrounded by fibrous tissue. Occasionally cirrhosis of this type involves a larger portion of the liver, as in 1 of the cases previously reported [1b] (case XIX). Several cases of biliary cirrhosis associated with pancreatic fibrosis have been reported.[6b] It is not clear whether they all were on the basis of intrahepatic and partial biliary obstruction but this is possible, since none of the patients were described as jaundiced. Hypoplasia of the gallbladder is a frequent finding, and atresia of the cystic duct has been described in some of these cases. One of us [1b] erroneously assumed that the underdevelopment of the gallbladder necessarily indicated atresia of the cystic duct. In the previously mentioned recent case of meconium ileus, however, a hypoplastic gallbladder measuring 2 by 0.6 cm. was found, containing 1 to 2 cc. of thick translucent gray gelatinous material. The lower third of the gallbladder formed a multilocular cavity divided by thin partial septums. The lumen was continuous, however, and communicated with the common duct through a small but patent cystic duct. It seems probable that the hypoplasia

of the gallbladder is the result of obstruction to inflow of bile because of abnormal secretion of the mucosa of the gallbladder, and that atresia of the cystic duct, when present, is secondary in the same manner that occlusion of the pancreatic duct is secondary to abnormalities of pancreatic secretion.

4. *Lesions in the Respiratory Tract.*—The pulmonary lesions have been amply described by a number of authors. They consist of a chronic purulent bronchitis, often associated with bronchiectasis and with terminal bronchiogenic abscesses; hemolytic Staphylococcus aureus is usually if not always the infecting agent. Their relation to the pancreatic lesion is not clear. The pulmonary lesions have been considered due to congenital bronchiectasis, to vitamin A deficiency secondary to steatorrhea,[1b] to an abnormality in the bronchial secretions comparable to that believed to cause the pancreatic lesion [4b] or to a general infection of unknown nature which involves both the pancreas and the bronchi.[2] It is quite unlikely that the bronchiectasis is congenital, since it is not found in infants dying in the neonatal period of meconium ileus or during the first two months of bronchopneumonia and purulent bronchitis. The present series includes 1 case of death from bacteremia at 31 days in which the lungs showed the interstitial pneumonia usually associated with bacteremia but the bronchi were normal. Moreover, the degree of bronchiectasis shows some correlation with the age of the patient, and there is adequate explanation for it in the chronic cough. The evidence is against the hypothesis that the pancreatic lesion is the result of infection; hence a common infectional origin for the pancreatic and the bronchial lesions is unlikely. The other two hypotheses deserve more serious consideration.

Ample evidence of poor absorption of vitamin A by these patients is provided by low serum levels, poor absorption curves and occasional areas of squamous metaplasia of the bronchial epithelium. It is true that the squamous metaplasia never affects the majority of the bronchi and is often absent. A major functional change may well precede the anatomic one; loss of cilia or of their activity may be postulated. It is difficult to refute the arguments in favor of the hypothesis that vitamin A deficiency contributes to the pulmonary lesion. Vitamin A deficiency resulting from inadequate intake, as seen in the Orient, does not however result in purulent staphylococcic bronchitis or even in pneumonia [11]; and the pulmonary involvement is not characteristic of steatorrhea due to celiac disease or sprue, both of which show steatorrhea and vitamin A deficiency. The purulent bronchitis of pancreatic deficiency must therefore be due to some other cause or to two or more factors which consistently occur together and of which vitamin A

11. Scott, A.: Personal communication to the authors.

deficiency is one. In a disease in which the defects in nutrition are such a major factor and in which the utilization of protein and of fat is about equally involved [12] the lack of some food substance or substances in addition to vitamin A may constitute the pathogenic factor. A somewhat less reasonable hypothesis is that suggested by Farber,[4b] that the secretions of the bronchial mucosa are defective in a manner similar to the pancreatic secretion. Against this, two observations may be marshalled. One of these is that the bronchial glands appear normal in most cases; only in occasional cases are ducts found which provide morphologic evidence of pathologic change. The other is the fact that bronchitis has not appeared in those cases in which an appropriate diet was started before the onset of the first respiratory symptoms. Moreover, bronchitis, once established, has decreased or disappeared in a fair series of cases with dietary therapy used alone or in association with chemotherapy. It seems probable that the pulmonary infection is secondary to the nutritional difficulty resulting from lack of pancreatic function. Vitamin A deficiency contributes to it, but some other factor or factors should be assumed and should be searched for.

COMMENT

On the basis of the evidence just presented, it is our present opinion that cystic fibrosis of the pancreas represents the commonest manifestation of a hereditary disease which may also involve the intestinal glands, the intrahepatic bile ducts, the gallbladder and occasionally other epithelial glands and which has as its primary feature the production of abnormal secretion of these glands, the morphologic features being secondary. The cases in which the clinical picture of congenital intestinal obstruction is presented usually, if not always, are cases of meconium ileus, often complicated by volvulus or peritoneal adhesions, and the meconium is believed to be abnormal because of lack of normal pancreatic function.[4a] The pulmonary infection is the result of the nutritional deficiency, and one factor contributing to it is poor absorption of vitamin A. If this concept of the disease, as based on a congenital and hereditary defect of the secretion of a number of types of glands, is correct, the disease is comparable to those presenting evidence of a congenital defect of an enzyme system, of which diabetes, glycogen storage disease and the various lipid storage diseases are familiar examples.

The incidence of fibrocystic disease of the pancreas among siblings approximates that expected of a recessive trait. Several considerations cast some doubt on the hypothesis that the disease occurs as an uncom-

12. Andersen, D. H.: Celiac Syndrome: III. Dietary Therapy for Congenital Pancreatic Deficiency, Am. J. Dis. Child. **70**:100-113 (Aug.) 1945.

plicated recessive one. The incidence of a gene in the general population must be fairly high if a lethal recessive trait is to appear frequently unless mutation and hence new appearance of the gene are common. The incidence of fibrocystic disease of the pancreas in the general population may be estimated from the fact that the diagnosis has been made in about 3 per cent of postmortem examinations in several children's hospitals in this country, including the Babies Hospital of New York. If it be assumed that this represents the incidence among all deaths of infants and children in New York, the incidence among live births can be calculated from the vital statistics of this city and state. Calculations based on the number of live births and the number of deaths under the age of 5 years in New York city for the years 1934 through 1938 [13] give an incidence of 1.82 per thousand live births; on the basis of the census figures for 1939 [14] for live births and deaths under the age of 14 years in New York state, the incidence is 1.73 per thousand live births. The disease is therefore moderately infrequent. An uncomplicated recessive trait which is lethal would tend to die out rapidly at this level, and future observations will be of interest.

A second relevant fact is the occurrence of the disease in the majority of siblings in a fair proportion of the affected families. This circumstance is not expected if the trait in question be a simple recessive one, and it provides a potent argument in favor of the hypothesis that more than one factor is required for the appearance of the disease. This implies that the factor for the disease may sometimes occur unexpressed and that the actual appearance of the disease in persons carrying this factor may be suppressed or stimulated by some other hereditary or environmental factor. This would provide an explanation of the variations in severity of the disease picture. The observed facts accord better with the hypothesis that two or more factors are involved than with the view that the disease occurs as a purely recessive trait dependent on a single gene.

SUMMARY AND CONCLUSION

Cystic fibrosis of the pancreas occurs among siblings, twins and more distant relatives with a distribution which is compatible with the hypothesis that it is carried as a relatively infrequent hereditary trait.

13. Emerson, H., and Hughes, H. E.: Population, Births, Notifiable Diseases and Deaths: Assembled for New York City, New York, 1866-1938, from Official Records, New York, De Lamar Institute of Public Health, College of Physicians and Surgeons, Columbia University, 1941.

14. Vital Statistics of the United States, 1939: Part I. Nativity and Mortality Data for the United States, Tabulated by Place of Occurrence with Supplemented Tables of Hawaii, Puerto Rico and the Virgin Islands, United States Department of Commerce, Bureau of the Census, 1941, pp. 59-292.

Evidence for this conclusion is based on a report of 48 cases in which the history of the sibling is known and on the family pedigrees in 20 of these cases and also on 56 cases in the literature in which information as to siblings is given. Although the incidence among siblings approximates the 25 per cent expected of a mendelian recessive trait, the distribution of the cases in families suggests that the disease, although hereditary, requires more than one factor for its expression. This hypothetic factor is as yet unknown.

The lesion in the pancreas is not a malformation in the true sense of the word but appears in the latter part of pregnancy. It probably results from an abnormality of the acinar secretion. A comparable disturbance is also found in the liver, the gallbladder and the intestines and possibly in other glands.

The congenital intestinal obstruction often associated with pancreatic fibrosis is probably the result of failure of pancreatic function, with secondary changes in the meconium, often complicated by volvulus or congenital peritoneal adhesions. The latter two conditions frequently tend to distract attention from the meconium ileus.

Evidence is presented in favor of the view that the pulmonary lesion begins after birth and is primarily the result of nutritional deficiency.

CONGENITAL DUODENAL OBSTRUCTION

Roentgen Diagnosis by Insufflation of Air

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IN recent years there has been a significant improvement in the results of the surgical management of congenital duodenal obstruction. In November 1945 Swenson and Ladd [1] reported 21 cases of intrinsic duodenal obstruction in the newborn, with 13 recoveries after operation. At the same time they reported 30 cases of extrinsic obstruction, with 26 recoveries. This record is in sharp contrast to that existing only two decades ago. In 1922 Davis and Poynter [2] presented 392 cases of congenital intestinal obstruction of all parts of the intestinal tract above the anus. In this survey of the literature, based on observations either at autopsy or operation, there were only 2 recoveries, a mortality of almost 99.5 per cent.

This striking decrease in mortality can to a considerable extent be attributed to the early roentgenographic diagnosis of these developmental anomalies. Swenson and Ladd [1] emphasized that "not only is the mortality in a given case directly related to the promptness of diagnosis and treatment, but the period of recovery and convalescence in the hospital is decreased." Ladd [1] has shown that an infant presents a better surgical risk during its first forty-eight hours than it does a week later. Moreover, perforation may occur within the first two days after birth. Surgical intervention should therefore be undertaken as soon as possible.

The roentgenologic diagnosis is usually made either by the use of barium sulfate as a contrast medium or by means of plain roentgenograms of the abdomen in which swallowed air is the contrast substance.

Read before the New York Academy of Medicine, Section of Pediatrics, Feb. 14, 1946.

From the Radiologic Service of Dr. Milton G. Wasch and the Pediatric Service of Dr. Benjamin Kramer, The Jewish Hospital.

1. Swenson, O., and Ladd, W. E.: Surgical Emergencies of the Alimentary Tract of the Newborn, New England J. Med. **233**:660 (Nov. 29) 1945.

2. Davis, D. L., and Poynter, C. W. M.: Congenital Occlusions of the Intestines with Report of a Case of Multiple Atresia of the Jejunum, Surg., Gynec. & Obst. **34**:35 (Jan.) 1922.

White and Collins [3] stated that there should be no hesitation in using a thin mixture of barium sulfate. However, Saunders and Lindner [4] and Ladd and Gross [5] warned that barium sulfate remaining in the gastrointestinal tract may plug the anastomotic stoma to be created in a future short-circuiting procedure. They suggested not only that extremely small quantities of barium sulfate be used but also that after the diagnostic procedure the stomach be thoroughly washed. Four days after use of barium sulfate for roentgenologic diagnosis Lee [6] found the major portion of the contrast medium still in the stomach and duodenum. Neuhauser [7] stated that there is serious danger of aspiration of barium sulfate when an infant is vomiting and that the resulting pneumonia is severe. Swenson and Ladd [1] concluded that "barium should be reserved for rare conditions in dealing with infants" and that it need never be used for intestinal obstruction.

The alternate method is the use of plain roentgenograms of the abdomen. In the case of newborn infants with congenital intestinal obstruction, Cohen [8] stated that plain roentgenograms will for the most part give sufficient information for a definite diagnosis. Air is seen to fill the portion of bowel above the site of obstruction, while no air is visible in the intestines beyond. This method, however, is likewise not without limitations. If the examination is made within the first twelve to twenty-four hours, the stomach and duodenum may be only slightly dilated. Should any of the previous feeding not have been vomited and remain in the stomach, the air normally ingested with the feeding may form a gastric bubble in the cardiac end of the stomach. The duodenal curve may therefore be poorly outlined by air. In this event, though the absence of air in the distal small intestine will suggest the diagnosis, an accurate localization of the site of obstruction will not be possible. This is demonstrated in a case (fig. 1) from the files of this hospital.

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3. White, C. S., and Collins, J. L.: Congenital Duodenal Obstruction, Arch. Surg. **43**:858 (Nov.) 1941.

4. Saunders, J. B., and Lindner, H. H.: Congenital Anomalies of the Duodenum, Ann. Surg. **112**:321 (Sept.) 1940.

5. Ladd, W. E., and Gross, R. E.: Abdominal Surgery of Infancy and Childhood, Philadelphia, W. B. Saunders Company, 1941, p. 30.

6. Lee, W. E., in discussion on Stetten, DeW.: Duodenojejunostomy for Congenital, Intrinsic, Total Atresia at the Duodenojejunal Junction, Ann. Surg. **111**:583 (April) 1940.

7. Neuhauser, E. B. D., cited by Swenson and Ladd.[1]

8. Cohen, P.: Congenital Intestinal Obstruction, with Special Reference to the Value of the Plain Roentgenogram for Diagnosis, Am. J. Dis. Child. **61**:135 (Jan.) 1941.

During roentgenologic studies in which 200 to 300 cc. of air was introduced into the stomachs of infants, Soveri [9] noted that the empty stomach can evacuate this quantity of air into the intestines within half an hour. Much of it is passed within five minutes. If the small intestine is empty, the air passes completely through in one to two hours. These studies, together with those of Wasch and Epstein [10] on the use of insufflation of air in the diagnosis of tumors of the cardiac end of the stomach, suggested the present method for the diagnosis of congenital intestinal obstruction.

Fig. 1.—Limitations of a plain roentgenogram in revealing the location of an obstruction (a case of jejunal atresia below the proximal quarter, confirmed at necropsy). *A*, plain roentgenogram showing two collections of air, one in the stomach, the other probably in the small intestine. The site of obstruction is not demarcated. *B*, roentgenogram of same patient two hours after a barium sulfate meal showing the dilated duodenum and proximal portion of the jejunum. The end of the barium column indicates the site of obstruction.

PROCEDURE

After plain roentgenograms of the abdomen are taken, a Levin tube of a size for infants is passed into the stomach, and the gastric contents are aspirated. Air, the contrast medium employed, is then introduced

9. Soveri, V.: Der Verlauf der Luft durch den Verdauungskanal des Säuglings, Acta pædiat. (supp. 3) **23**:1, 1939.

10. Wasch, M. G., and Epstein, B. S.: The Roentgen Visualization of Tumors of the Cardia, Am. J. Roentgenol. **51**:564 (May) 1944.

slowly under fluoroscopic observation. Sixty to 90 cc. is usually sufficient to produce satisfactory filling of the stomach and upper portion of the intestine. The infant is rotated to the left under the fluoroscopic screen so that the course of the posteriorly situated duodenum can be traced. "Spot" roentgenograms are taken in such positions as are found to project the duodenum most advantageously. At the conclusion of this procedure, air which has not already been eructated is removed by aspiration, and the tube is withdrawn. The differentiation of complete obstruction from minimal patency may be aided by serial roentgenograms at hourly intervals. These are studied for evidence of progression of the air through the bowel.

Two cases of duodenal obstruction, in one intrinsic and in the other extrinsic, studied by this method, are presented.

REPORT OF CASES

CASE 1.—M.R.B., a white girl, was born on Aug. 22, 1945, the fourth child of a 34 year old mother. Gestation and labor were marked by polyhydramnios, necessitating artificial rupture of the membranes. The baby weighed 6 pounds 1 ounce (2,750 Gm.) and was delivered spontaneously after a labor of nineteen hours.

Physical Examination.—The baby had a definitely mongoloid appearance, with epicanthic folds and flattening of the nose. Her lips and extremities were cyanotic. The cry was feeble and infrequent. There was generalized hypotonia. Dulness, diminished breath sounds and inconstant crepitant rales were noted over the upper halves of both pulmonary fields. A precordial blowing systolic murmur was heard by some observers. The abdomen was flat and soft. No masses were palpable, and no tenderness was elicited. Bilateral talipes equinovarus was present.

Hospital Course.—The infant took her feeding fairly well but vomited frequently and in amounts apparently equal to those ingested. The vomitus was at times milky and contained mucus. Occasionally it consisted of brown fluid. She passed many small meconium stools. The continuous parenteral administration of fluids by means of bone marrow infusion was started on the third day of life. The following day a plain roentgenogram (fig. 2 *A*) of the abdomen showed air in the stomach but none in the small or the large intestine. There was atelectasis of both upper pulmonary fields. A Levin tube was passed into the stomach, and continuous Wangensteen suction was instituted. On the fifth day of life another roentgenographic study (fig. 2 *B*), following the introduction of 90 cc. of air through the Levin tube, revealed that the column of air stopped abruptly just beyond the first portion of the duodenum. Two hours later another roentgenogram (fig. 2 *C*) showed no further progress of air through the intestine. A diagnosis was therefore made of obstruction, probably atresia, beyond the first portion of the duodenum. Consent to perform an operation was not obtained until the seventh day of life, when a laparotomy was performed.

Observations at Operation and Procedure.—The stomach was dilated, and the first portion of the duodenum ended abruptly in a bulbous protuberance. The segment of duodenum between the latter and the point of entrance of the common bile duct appeared to be absent. The remainder of the small and of the large intestine was intact. The mesentery did not have its usual attachment to the posterior parietal wall but stemmed from a single stalk at the origin of the superior mesenteric vessels. There was malrotation of the colon, with the cecum held high in the right

upper quadrant of the abdomen by bands which traversed the second portion of the duodenum to join the posterior parietal peritoneum.

After the bands were divided, a lateral anastomosis, joining the jejunum to the anterior portion of the duodenum, was performed.

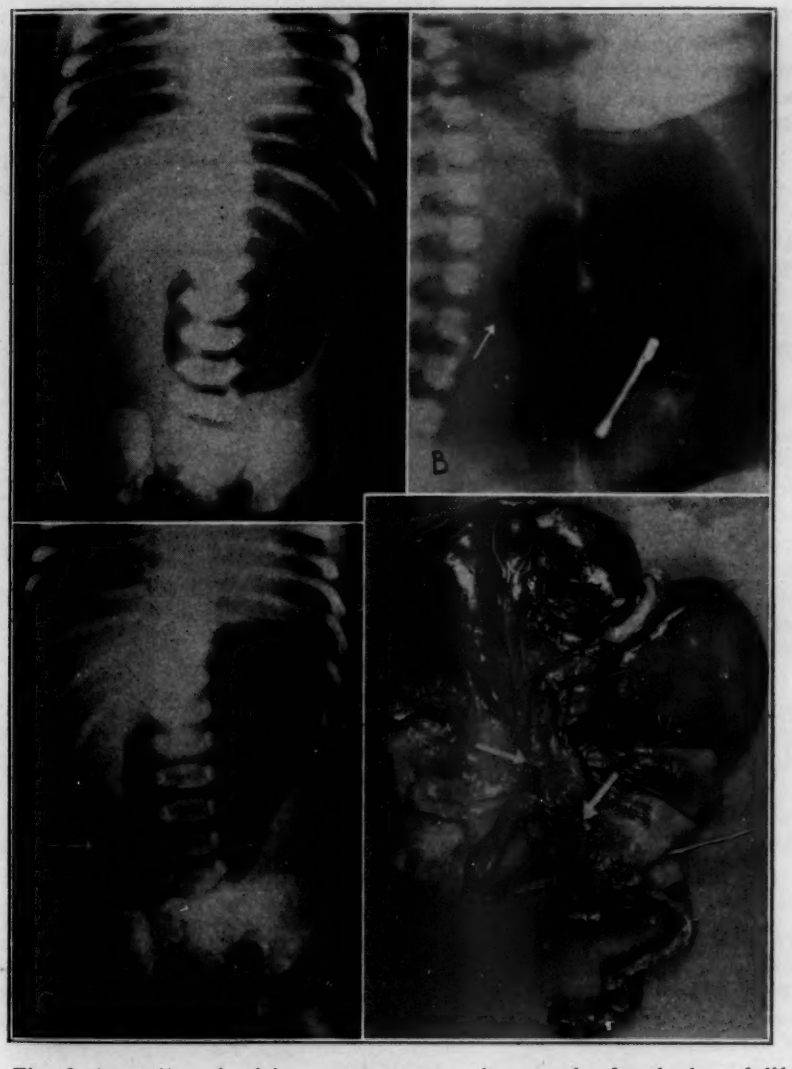

Fig. 2 (case 1).—*A*, plain roentgenogram taken on the fourth day of life, showing a dilated stomach and the absence of air beyond. *B*, right oblique film after insufflation of 90 cc. of air. The proximal portion of the duodenum is well outlined and distended (arrow). *C*, roentgenogram two hours later. No air has passed beyond the point of obstruction (arrow). *D*, necropsy specimen: atresia, 2 cm. in length, of the second portion of duodenum proximal to the ampulla. The arrow on the right indicates the dilated first portion of the duodenum; the arrow on the left indicates the common bile duct entering the duodenum. Note the absence of the second part of the duodenum between these points. The probe passes behind the site of the duodenojejunostomy.

Postoperative Course.—Seven hours after the operation the infant became distended and remained so despite Wangensteen suction. Her condition progressively declined, and she died on the ninth day of life, thirty-five hours after operation.

Postmortem Observations.—The stomach and the first portion of the duodenum were much dilated. Two centimeters beyond the pylorus the duodenum narrowed to become a fibrous band, 0.1 cm. in diameter, which extended for a distance of 2 cm. At this point the duodenum resumed its normal size and course. The external biliary system was normal, and the common bile duct entered the second portion of the duodenum just distal to the area of atresia. The anastomotic stoma was patent. Microscopic examination of the fibrous band revealed it to be a solid cord.

CASE 2.—L. L., a white girl, was admitted to the hospital on Dec. 19, 1945, forty-four hours after birth, because of inability to retain food and failure to pass

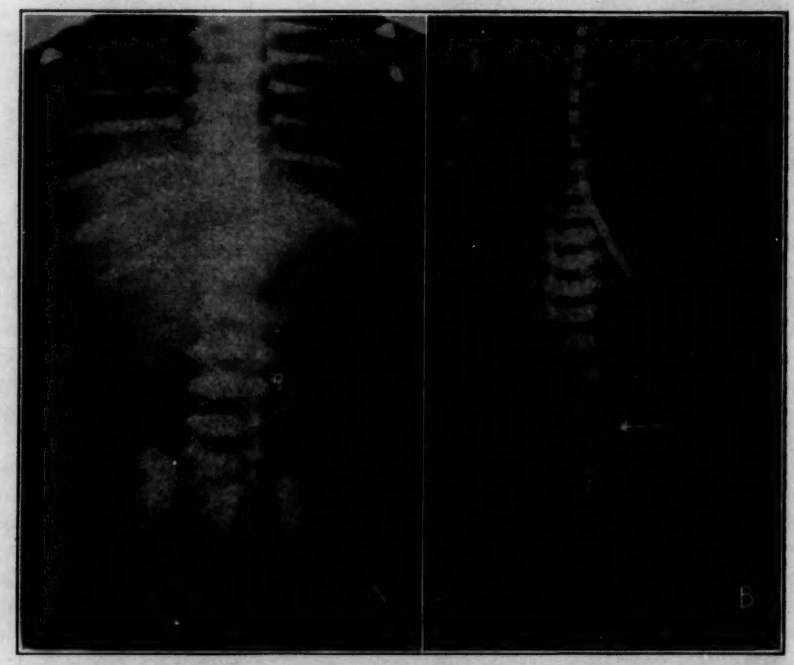

Fig. 3 (case 2).—*A*, plain roentgenogram taken forty-four hours after birth. The stomach and duodenum are incompletely outlined by air. The site of the obstruction is not evident. *B*, plain roentgenogram after the introduction of 60 cc. of air. The stomach and duodenum are completely outlined to the duodenojejunal junction (arrow). Note the absence of air beyond this point, indicating the site of obstruction.

a stool since birth. She was delivered at term with the aid of low forceps. The birth weight was 6 pounds (2,720 Gm.). She took feedings readily but vomited after each. An enema on the morning of admission yielded a dark brown fluid but no meconium.

Physical Examination.—The infant was well nourished and not dehydrated. The abdomen was moderately distended but soft. No peristaltic waves were visible, and no masses were palpable. She had lost 4 ounces (113 Gm.) since birth.

Hospital Course.—A plain roentgenogram (fig. 3 *A*) of the abdomen at the time of her admission revealed a slightly enlarged air bubble in the cardiac end of the stomach and another extremely small collection of air to the right of the fourth lumbar vertebra. A Levin tube was passed and 15 cc. of dark green fluid was aspirated. After the introduction of 60 cc. of air (fig. 3 *B*), the stomach was found to be of average size and configuration. The duodenum was clearly portrayed throughout its course and appeared normal. The air column ended abruptly, however, at the duodenojejunal junction, and diagnosis of obstruction at this site was made.

The infant continued to regurgitate large amounts of green fluid and passed no stool. Fluids were administered by continuous intravenous drip, and twelve hours after admission, fifty-six hours after birth, a laparotomy was performed.

Operative Observations and Procedure.—The stomach and duodenum were decidedly enlarged. The small intestine was completely collapsed. At the region of the ligament of Treitz a mass covered by large veins was palpated. No attempt was made to explore because of the overlying vessels. Extrinsic compression of the duodenojejunal junction or atresia of the duodenum was assumed to be the cause of obstruction. Several jejunal loops were adherent to the mass. A gastroenterostomy was performed, a single layer of interrupted silk sutures being used.

Postoperative Course.—The infant received supportive treatment in the form of continuous intravenous administration of fluids and small transfusions of blood and plasma. Feedings were instituted forty-eight hours after operation, and vomiting subsided gradually. On the third day after operation she passed her first stool. The postoperative course was complicated by the development of atelectasis of the upper lobe of the right lung, which cleared after five days. A plain roentgenogram of the abdomen six days after the operation revealed the small bowel well filled with air. A further complication was the development of diarrhea, which was treated by a short period of starvation followed by feedings of protein milk. The infant was discharged thirteen days after operation, weighing 6 pounds 1 ounce (2,750 Gm.). There was no vomiting, and feedings were taken well.

The infant was admitted to another hospital on Jan. 7, 1946, eighteen days after the operation, because of a loss in weight of 8 ounces (227 Gm.) and diarrhea. Although the abdomen was soft on admission and the infant was passing four stools daily, an obstruction appeared to develop on the fifth hospital day, when there was abdominal distention and vomiting. A laparotomy performed on that day revealed free peritoneal pus and a large abscess involving many loops of necrotic bowel. Peritoneal drainage was instituted, but the infant died three days later.

Postmortem Observations.—Volvulus of the entire small bowel due to rotation of the mesentery around its root was found. The small intestine was necrotic and perforated. Generalized peritonitis was present. The mass noted at the original operation was found to be due to the rotated abnormal mesentery. The obstruction was caused by a kink at the duodenojejunal junction.

COMMENT

The use of injected air as a contrast medium appears to have several advantages. The method is safe, rapid and without untoward consequences. The possibility of aspiration pneumonia and of mechanical intestinal obstruction, which exists when barium sulfate is used, is eliminated. In the absence of air elsewhere in the bowel, air provides an excellent contrast substance which clearly outlines the location and

extent of the patent bowel. Fluoroscopic control eliminates the possibility of overdistention of the stomach. Finally, when the roentgenograms have been taken the contrast medium can be withdrawn, leaving no residuum and producing no after effects.

SUMMARY

Early roentgenographic examination in all cases of suspected congenital duodenal obstruction is highly desirable. Insufflation of air into the stomach under fluoroscopic control permits accurate localization of the site of the lesion. It eliminates the dangers of the administration of barium sulfate and is frequently more accurate than the plain roentgenogram of the abdomen. Two cases of congenital duodenal obstruction are presented in which the roentgenologic localization was verified at operation and postmortem examination.

We were assisted in the preparation of this paper by Dr. Milton G. Wasch and Dr. Benjamin Kramer. Dr. Samuel Silber and Dr. Rudolf Nissen granted us permission to report these cases.

Case Reports

SPONTANEOUS CHYLOTHORAX IN INFANCY

Prognosis and Management

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Chylothorax in infants is so rare that there is no consensus on its prognosis and management. The meager data available indicate that the prognosis of spontaneous chylothorax of the acquired type is much better than that of congenital type. The same meager data afford no optimism for surgical treatment of chylothorax in infants, inasmuch as no record of successful surgical correction of chylothorax in infancy was found. An instance of spontaneous chylothorax is reported, and available data are reviewed for light on management and prognosis.

REPORT OF A CASE

E. D. G., an 8 week old white baby girl, was admitted to the University Hospital with a history of a normal delivery at term and an entirely normal progress to one week prior to admission. Her birth weight was 9 pounds (4,080 Gm.), and at 7 weeks she weighed 12 pounds 5 ounces (5,585 Gm.). She had been given a formula of cow's milk, Karo syrup and water, with adequate vitamin supplements.

The first evidence that the infant was not entirely well came one week before admission, when she was noted to have some irregularity of breathing, described by the mother as sighing in character with the infant trying apparently to take a deep breath. It was also noted that the child at times appeared to have an anxious or disturbed look. The first definite evidence that she was ill came on the evening of the fourth day before admission to the University Hospital when at the 6 p. m. feeding time, but before being fed, she was observed to be in distress and to be breathing with difficulty. The respiratory rate was rapid; there was some retraction of the upper abdominal and suprasternal areas with each respiration, and the mother said the breathing was "wheezing." The infant's color was good, and there was no elevation of temperature. These signs of respiratory difficulty continued throughout the night, and the following day one of us (L. F. F.) saw the child and by clinical observations and roentgenologic examinations determined the presence of fluid in the right side of the chest. Thoracentesis revealed a milky fluid, which was thought to be chyle. About 170 cc. of this fluid was removed, by two thoracenteses, during the two days immediately preceding the infant's referral to the University Hospital.

Physical examination on her admission to the hospital revealed a well developed, well nourished infant, whose weight was 11 pounds 12 ounces (5,330 Gm.) and whose length was 23 inches (58.4 cm.). Her temperature was 99.8 F. by rectum, and except for the rapid, somewhat labored breathing she appeared

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quite normal. Her color was good. She was somewhat irritable when handled but did not cry much, as crying was difficult to manage because of the dyspnea. The only abnormal physical conditions related to the chest and consisted of a flat percussion note over the right hemithorax, both anteriorly and posteriorly. There was an apparent shift of the heart to the left, and the breath sounds were loud over the left side of the chest and muffled to absent over the right side of the chest. The respiratory rate was 60 per minute; the breathing was rather shallow in spite of its labored nature, and there was retraction of the suprasternal and epigastric regions with each inspiration.

Thoracentesis through the sixth intercostal space in the right posterior axillary line yielded a white, opaque fluid almost exactly resembling milk. Two hundred cubic centimeters of this came readily through the cannula, with complete relief of the dyspnea.

Study of the fluid removed showed it to be sterile and, in the 6 specimens tested, to vary as to specific gravity from 1.008 to 1.130. A specimen obtained by thoracentesis on June 11, 1945 had a specific gravity of 1.130, a cholesterol level of 102 mg. per hundred cubic centimeters, a total fat content of 1,435 mg.

TABLE 1.—*Amounts of Chyle Obtained by Thoracentesis From Onset to Spontaneous Closure*

Date	Amount, Cc.	Date	Amount, Cc.
6/3	70*	6/10	150
6/4	100*	6/11	240
6/5	200	6/12	230
6/6	150	6/13	165
6/7	150	6/14	135
6/8	375†	6/15	0
6/9	180	6/16	100
Total			2,245

* These thoracenteses before admission to University Hospital.
† Two thoracenteses on June 8, 1945.

and a protein content of 3.275 Gm. The last figure is calculated from a nitrogen content of 0.524 Gm. per hundred cubic centimeters of fluid and presupposes all the nitrogen to be from protein. Another sample, obtained on another day, had about the same cholesterol content—113 mg. per hundred cubic centimeters—but was considerably lower in protein—1.73 mg. per hundred cubic centimeters. Albumin made up 1.34 mg., and the remainder—0.39 mg.—was assumed to be globulin.

As shown in table 1, repeated thoracentesis was necessary (approximately one a day) during the patient's hospital stay of two weeks: a total of 2,245 cc. of chyle was removed before the chylothorax fistula closed spontaneously. Throughout her hospital stay the patient remained afebrile, with a leukocyte count varying between 4,900 and 8,000 per cubic millimeter with a normal differential count. Results of urinalysis were normal, and a Kahn test elicited a negative reaction. Sulfadiazine, 0.065 Gm., was given every four hours in the hope that it would prevent infection arising from accidental introduction of bacteria into the pleural cavity during the repeated thoracenteses; it was hoped that it would prevent nosocomial infection also.

It is of interest to note that the spontaneous cessation of the leakage of chyle into the thoracic cavity coincided with the onset of a mild diarrhea. It is impossible to postulate a connection between these two events, and the coincidence would

not have been mentioned here had not Wessel[1] noted in the case of a younger infant who recovered from chylothorax spontaneously exactly the same time sequence between the final thoracentesis and the onset of diarrhea. In the case here reported, the diarrhea was mild and responded readily to boiled skim milk feedings for two days, after which the patient was successfully returned to her previous formula. With the exception just noted the infant was on a formula composed of reconstituted powdered milk, 30 ounces (850 Gm.), and corn syrup, 1½ ounces (43 Gm.), throughout her hospital stay. Vitamin supplements consisted of ascorbic acid, 50 mg. daily, and oleovitamins A and D, 6 drops daily. The caloric intake was between 55 and 60 calories a day, and the fat content of the formula was approximately that of half-skimmed milk. Selection of a relatively low fat, high carbohydrate formula was based on the premise that such a feeding might lessen the formation of chyle.

COMMENT

In spite of its relative fragility the thoracic duct seldom suffers tears or rupture if one may judge from the published reports of cases of chylothorax and chyloperitoneum. After careful study of the literature up to 1935, Yater[2] estimated that cases of nontraumatic chylothorax were twice as numerous as those attributable to trauma. In the former group (nontraumatic) he included those caused by neoplasms which either directly invaded the thoracic duct or eroded it by pressure. Second to neoplastic growths. Yater placed inflammatory lymph gland masses as causes of erosion of the thoracic duct or one of its branches or collaterals; tuberculous nodes were the commonest of these. Table 2 reveals that among the cases of chylothorax in infants the disease occurs "spontaneously" in the majority of instances as far as can be determined.

The possibility of surgical treatment in the case herein reported was considered, but fortunately the patient's favorable course made surgical intervention unnecessary. That surgical intervention will fail in at least some of the cases of infants is indicated by a statement of Forbes.[3] Speaking of an autopsy on an infant 6 weeks of age who died of chylothorax he said, "Careful search, both in the gross and in tissue sections, failed to reveal the thoracic lymph duct or the cisterna chyli." The experience of Little, Harrison and Blalock emphasized that in certain cases chylothorax is apparently caused by thrombosis of veins into which the thoracic duct or its collaterals empty. In such cases the possibility of finding on surgical exploration a situation which can be corrected by operation seems rather remote. One is forced to conclude from recorded experience in this connection that surgical intervention is not very promising in chylothorax. That the thoracic duct can be ligated without unfavorable sequelae would be inferred from experimental work on dogs.

NUTRITIONAL CONSIDERATION IN CHYLOTHORAX

With respect to protein and fat, chyle tends to have about the same composition as half-skimmed cow's milk. Removal of large amounts of chyle by paracentesis will if long continued impair nutrition. Of all the constituents of chyle it is obvious that loss from the body of proteins and fat (and fat-soluble vitamins)

1. Wessel, M. A.: Chylothorax in a Two-Weeks-Old Infant with Spontaneous Recovery, J. Pediat. **25**:201 (Sept.) 1944.

2. Yater, W. M.: Non-Traumatic Chylothorax and Chylopericardium, Ann. Int. Med. **9**:600 (Nov.) 1935.

3. Forbes, G. B.: Chylothorax in Infancy, J. Pediat. **25**:191 (Sept.) 1944.

constitutes the most serious interference with nutrition. Table 3 gives results of analysis of chyle by various investigators.

Several writers have reported the intravenous transfusion of chyle, obtained by paracentesis, in an effort to minimize nutritional impairment. Apparently

TABLE 2.—*Chylothorax in Infants (Under One Year)*

Reported by	Age	Sex	Cause	Located	Result
1. Everhart and Jacobs: J. Pediat. **15**: 558, 1939	15 days	F	Spontaneous	Right side of thorax	Died
2. Stewart and Linner: Am. J. Dis. Child. **31**: 654, 1926	4 days	..	Spontaneous	.....	Died
3. Hilgenberg: Monatschr. f. Geburtsh. u. Gynäk. **83**: 225, 1939	15 days	F	Spontaneous	Right side of chest	Died
4. Janet, Bœgner and Laquerrière: Bull. Soc. de pédiat. de Paris **34**: 577, 1936	3 wk.	M	Spontaneous	Right side of chest	Recovered
5. Janet, Bœgner and Laquerrière: Bull. Soc. de pédiat. de Paris **34**: 577, 1936	2 mo.	..	Spontaneous	.....	Recovered
6. Pisek: Arch. Pediat. **34**: 929, 1917	2 mo.	F	Spontaneous	.....	Recovered
7. Gironcoli: Pediatria **45**: 720, 1937	2 mo.	F	Tuberculous node	Right side of chest	Died
8. Muttermilch: Ztschr. f. klin. Med. **46**: 122, 1902	5 mo.	..	Trauma, fall from bed	Right side of chest	Recovered
9. Foley: Prensa méd. argent. **20**: 62, 1933	9 mo.	..	Spontaneous	.....	Recovered
10. Jennings and Rich: Arch. Pediat. **25**: 195, 1908	9 mo.	..	.....	.....	Recovered
11. Forbes [3]	6 wk.	F	Spontaneous	Bilateral	Died
12. Wessel [1]	2 wk.	M	Spontaneous	Right side of chest	Recovered
13. Case reported in this article	8 wk.	F	Spontaneous	Right side of chest	Recovered

TABLE 3.—*Analyses of Chyle in Chylothorax and Chyloperitoneum*

Chemistry	Our Patient	Wessel	Little et al.	Yater	Forbes
Specific gravity	1.008 to 1.130	....	.....	....	1.012
Total protein, Gm. per 100 cc	3.275 1.73	3.38	3.16 thorax 3.08 abdomen (16 determinations)	2.78	2.97 2.72
Albumin, Gm. per 100 cc	1.34	....	1.64 to 2.98	2.07	2.59 2.20
Globulin, Gm. per 100 cc	0.39	....	0.18 to 1.92	1.71	0.35 0.52
Total lipids, mg. per 100 cc	1,435	1,810 2.40*	450 to 3,100 (21 analyses on chyle from thorax and abdominal cavity)	....	489 1,261
Cholesterol, mg. per 100 cc	102 113	87.4 72.6*	143 to 181	80	48
Sugar, mg. per 100 cc	...	126	.....	....	...
Calcium, mg. per 100 cc	...	...	.....	....	9.3
Phosphorus, mg. per 100 cc	...	7.8	.....	....	6.2

* Patient on skim milk diet.
† Data obtained on chyle from thorax and from abdomen.

this procedure is not only feasible and safe when properly performed but has much to recommend it. Assuming aseptic precautions, it seems unlikely that

untoward results would follow such transfusions. Little and his associates,[4] who have apparently reintroduced intravenously a larger volume of chyle than any other group, made no mention of anticoagulant. They apparently reintroduced the chyle by means of a closed system: "the chyle being aspirated from the chest and then immediately injected intravenously." Forbes also reintroduced the aspirated chyle intravenously after testing it by subcutaneous injection. He used sodium citrate in a concentration of 0.25 per cent, presumably to prevent coagulation of the chyle. Little, Harrison and Blalock reported a case of chylothorax and chyloperitoneum in a 17 year old girl, who in a period of six months had 180,000 cc. of chyle removed from the chest and peritoneum and 22,500 cc. reintroduced by intravenous injection. These writers calculated that during nineteen months of illness this patient suffered a loss of 16,000 Gm. of protein in approximately 550 liters of chyle. During the special observation period of six months she lost approximately 25 Gm. of protein a day by way of chyle removed by paracentesis.

Recent reports of chylothorax in infancy by Forbes and Wessel include studies of fat-soluble vitamins in the chyle removed. These studies verify the assumption that fat-soluble vitamins A and D are lost in the chyle in appreciable quantities. Carotene did not appear in the chyle in significant amounts following its administration by mouth.

Several of the reports on chylothorax refer to the use of a low fat diet. In most of these, the selection of such a diet was not, as far as can be determined, based on any proof that such a diet reduced the formation of chyle, though it is easy to see how a decision to use low fat feedings naturally arises from the supposed natural function of the thoracic duct system—the collection and transport of nutrients from the small intestines to the blood stream. Schaefer[5] reported that a fat-free diet reduced the fat content of chyle, but he found no change following variation of the protein and the carbohydrate of the food intake.

It would appear that attempts to "dry up" the leakage of chyle or to reduce its production by underfeeding could not be long continued in view of the loss of protein, fat and calories in chylothorax and chyloperitoneum. Scientific evidence supporting the rationale of underfeeding is entirely lacking. An excess over calculated normal requirements of protein and carbohydrate sufficient to balance the loss from the removal of chyle should be attempted. The infant here reported on received 58 calories per pound (454 Gm.) per day by mouth. That this fell short of maintaining her in an adequate state of nutrition is shown by the lack of gain in weight for two weeks—she weighed exactly the same on discharge as on admission. She received 100,000 units of vitamin A parentally once a week.

In the case reported on by Little and his associates, the loss of protein and calories was so excessive and prolonged that the maintenance of satisfactory nutrition was impossible by oral feedings supplemented by transfusions of chyle. As these investigators pointed out, one of the problems in managing patients with chylothorax or chyloperitoneum is that of maintaining adequate protein nutrition (blood serum proteins and tissue proteins) in face of the constant heavy drain through loss of chyle. Amino acid preparations, both orally and intravenously administered, should be of value in this connection.

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4. Little, J. M.; Harrison, C., and Blalock, A.: Chylothorax and Chyloperitoneum, Surgery **11**:392 (March) 1942.

5. Schaefer, R.: Beiträge zur Kenntnis des Chylothorax, Deutsches Arch. f. klin. Med. **157**:69, 1927.

PROGNOSIS OF CHYLOTHORAX IN INFANCY

Study of table 2 indicates that the chances of spontaneous cure of chylothorax in infancy are better than 50 per cent if prognosis can be based on the outcome of 13 cases. Furthermore, if one supposes that in the first 3 cases in table 2 it was caused by congenital malformation or absence of a normal thoracic duct, a supposition based on the extremely early onset of chylothorax and supported by the fact that most careful examination both macroscopic and microscopic failed to reveal any evidence of a thoracic duct in case 1, it then becomes apparent that the prognosis in acquired chylothorax in infancy is probably fairly good—i.e., 2 deaths in 10 cases. Actually in all but 1 of the 9 cases of acquired chylothorax there was recovery, if case 7, in which the cause was erosion of the thoracic duct by a tuberculous lymph node, is excluded.

SUMMARY

A case of spontaneous chylothorax with recovery is reported. Study of reported cases indicates the probability of spontaneous cure of idiopathic chylothorax there was recovery, if case 7, in which the cause was erosion of the these patients.

Progress in Pediatrics

ROLE OF PSYCHIATRY IN A CHILDREN'S HOSPITAL SERVICE

Account of an Experiment in Integrating Psychiatry and Pediatrics in an Inpatient Service

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THERE is today widespread recognition among physicians and lay people alike that psychiatry is influencing modern medicine. Acceptance of many of the tenets of this comparatively new discipline has come slowly and unsystematically, often unconsciously and even unwillingly. There are still many blindspots in the recognition of the value of medical psychology. In contrast, there is at times an uncritical regard which amounts to evangelistic zeal in the new convert. The pediatrician, like his colleagues in other fields, not only is increasingly receptive to these changes in medicine but is desirous of benefiting from them; in terms of skill, knowledge and technical ability in medical psychology he usually finds himself wanting. Quite naturally he turns to others for help—first, for further self appraisal of his needs and second, for instruction in supplying these essentials. Experimentation in applying the principles of medical psychology to modern pediatric practice and to the teaching of pediatrics has been carried out in the New York Hospital and Cornell University Medical College since 1933, with the manifold assistance of the Commonwealth Fund and the cooperation of psychiatrists, pediatricians and social workers. It was not the aim of this combined pediatric and psychiatric undertaking to develop physicians as child psychiatrists, and, although at times the terms "pediatric psychiatrist" or "psychiatric pediatrician" have been used to designate conveniently those pioneer pediatricians who devoted a major portion of their time in bridging the gap between the two disciplines, the end in view has not been the development of a new specialty of "pediatric psychiatry." Instead, it was hoped that by providing new insight and new technics of patient care which could be incorporated and integrated into pediatrics this specialty might be modified and its function augmented, in keeping with the changes in

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modern medical progress. One aspect of the experiment in synthesizing pediatrics and psychiatry in the inpatient service of the New York Hospital is described in the following account.

HISTORY OF DEVELOPMENT

The introduction of psychiatry to the pediatric inpatient department of the New York Hospital came gradually, after its contributions had been found useful in the outpatient clinic. Its services there were first sought in occasional consultation with a psychiatrist, when children presented problems of behavior management in the community, home and hospital which, by exclusion, could not be explained on an "organic" basis and which could not be remedied by the usual pediatric practices. Infants and children who appeared mentally retarded as well as those who had convulsive disorders were also referred for psychiatric appraisal. The number of requests for such psychiatric aid increased with time, and with this came in 1939 the suggestion from the pediatric house officers and pediatricians-in-training that more time be spent in the discussion of emotional problems in the hospitalized patient which could not be satisfactorily interpreted through formal written reports alone. This suggestion, which revealed the progress which had been made in pediatrics from disbelief or vague interest in psychiatry to healthy query and better understanding of its function, helped to crystallize plans for the establishment of a psychiatric unit in the inpatient services of the Children's Clinic, which was supported financially and ideologically both by the department of pediatrics and by the department of psychiatry. The often expressed criticism that psychiatry is isolated from the rest of medicine and that its "private dialect" sets it still further apart was accepted as valid; hence the objectives of this new phase of psychiatric-pediatric development included the establishment of a basis for common communication and for an exchange of ideas, which would aid both medical disciplines to attain a better understanding of the processes of disease. With the aid of the Commonwealth Fund, the personnel was increased to include a pediatrician with special training in psychiatry, who would hold an appointment both in the psychiatric and in the pediatric department and would act as a liaison member between the two. The services of a psychiatric social worker and of a psychologist were also made available.

OBJECTIVES

With the extension of psychiatry from the pediatric outpatient department to the pavilions new questions arose which implied a broadening of the pediatric-psychiatric service. Teaching and service in pediatrics, with the individual child as subject, remained the goal, but the question was asked whether these functions could not be enhanced

by studying patients in the contrasting setting of the hospital as well as in that of the "outside," the home, the school and the clinic. It was planned, then, to make observations of the infant and child during this special period of their lives; to note the incidence, type and relation of emotional elements accompanying or stimulating physical illness and the part played by mental retardation; to gage the interest, ability and needs of the nursing and medical staffs for adequately dealing with the psychologic as well as the physical aspects of disease in those patients with whom they work many hours each day and whom they are helping to prepare again for a full life in the community; and to evaluate teaching methods which could best prepare the hospital staff for these new duties. It was hoped that this project would supply useful data about the growth and development of the child and about his feelings and reactions during illness and convalescence; that it would improve the care of children in hospitals, and that it would help define for the pediatrician and the nurse their roles in mental hygiene and child psychiatry.

METHODS

At the onset of the new program in 1939, emphasis was placed on the teaching aspects by the pediatricians-in-training, who requested aid in the early recognition, understanding and treatment of psychologic deviations in the children admitted to their care in the hospital. The questions raised by them showed that each had a desire to learn for himself (but not by himself) under guidance about his own patients. This proposal was agreeable to the teaching staff, who felt that true learning comes through doing and that only by training the pediatrician in this way could he better understand his own abilities and limitations and thereby handle at all satisfactorily the great case load of emotional problems, which seem increasingly to make up the bulk of pediatric practice. The phrase "applied psychiatry in pediatrics" describes well the nature of the program carried out in the past seven years.

The methods of guidance and instruction vary. In general, the attempt is made to keep the instruction at the levels of learning and of interest of the persons being taught; although these methods vary with each person, it is evident that the acceptance of new teachings about psychologic aspects comes more naturally when the material is presented along with the somatic elements. The daily round of the wards made by the staff of pediatricians, nurses and some medical students afford an excellent medium for such teaching. These rounds are conducted by the pediatric resident, and attendance is limited to the house staff with the one exception that the pediatrician with psychiatric training (hereafter referred to as the liaison physician) has been given the special privilege of daily attendance by the intern group. He has usually

functioned as an observer, limiting his discussion to occasions when he is called on for opinions and suggestions. From the standpoint of the liaison physician, such attendance serves several important purposes: It enables him to hear the anamnesis of new patients and the follow-up reports on old ones, as given by the house officers; it helps him to observe the patients in the ward setting and, in turn, to be seen and accepted as one of the pediatric staff, so that, should any child be referred for later study, he is regarded as a trusted friend instead of a suspected stranger; he is readily available for the discussion of the problems at hand, thus intergrating the psychiatric with the pediatric issues, and finally, his physical presence makes him acceptable as a member of the pediatric staff with a common interest in the care of the sick child.

Each physician is encouraged to make a personality study (and, in selected cases, a psychiatric appraisal) of his patients and to carry on those therapeutic procedures which he is capable of doing safely. He is offered time for individual conferences with the liaison physician for the discussion of psychogenesis, social survey, further investigation, general hospital and community management and special psychotherapy. These discussions are kept on a practical plane in terms of the reality situations. Arrangements are made to conduct these conferences in a leisurely and unhurried manner with an informal exchange of ideas. The press of time, the feeling that these meetings are obligatory, extra-curricular, "fancy" or not as important as the usual custom-tried hospital conferences (e. g. clinical-pathologic conferences), all militate against their success as teaching projects. When after these conferences the pediatrician still feels inadequate to evaluate accurately the psychologic aspects of a case, the child is referred to the liaison staff member for consultation. The technic of the consultation is as follows:

When the request for psychiatric appraisal is received, the child is usually already known to the consultant through contact on ward rounds. Appointments for interviews are next made with parents or parent surrogates, with the purpose of obtaining additional information about the child in his present illness, about his past history and personality and about the family history, in order to evaluate the role of the family and community setting in the child's difficulties. Often there is also a meeting in the hospital or in the home between the parents and the psychiatric social worker as a further aid in assaying social and economic influences. The older patient is usually seen alone two or three times by the liaison physician in his office in the Children's Clinic for a general discussion of hospitalization. Without the use of inquisitorial methods, or even of direct questioning, but rather as part of a

friendly and interested consideration of the child, there will sooner or later come up a discussion about the problems which stimulated psychiatric referral. Observation of the child in the hospital environment in relation with his fellow patients also tells much about his personality and his intelligence. The infant and the young child are played with, talked to and examined while in the crib and watched while at play with their fellows. From these observations definite conclusions as to their development, emotional, physical and intellectual, are reached. Many of the patients are then seen by the psychologist and given detailed psychometric studies. The majority are also observed in play by a trained diversional therapeutist, who reports their expressions of play activity as well as their verbal comments. The final formulation includes the opinions of those who studied the psychiatric, psychometric, social service and diversional therapy responses of the patient and their recommendations as to diagnosis and management. Treatment by house staff members is undertaken when feasible under the supervision of the liaison physician except in cases in which extensive psychiatric therapy is indicated; this is usually postponed until the patient has left the hospital. Where community agencies and educators play a part in the management of the patient after discharge from the hospital, conferences between their representatives and the pediatrician and the psychiatric team are arranged.

What might be called the formal means of instruction in this service, in contrast to the informal approaches just described, consist of conferences in pediatric psychiatry with the professors of pediatrics and psychiatry, the liaison staff member, the psychiatric social worker and, occasionally, the psychologist for discussion of the consultation reports of those patients who have been recently referred for detailed psychiatric and social service studies. These are regular monthly seminars of the entire pediatric staff, held for one hour and attended by pediatric practitioners as well as by full time staff members and by house staff groups, for the consideration of a current hospital case which after study has been found to illustrate some important teaching point in the care of infants and children. The seminar is conducted as follows: Each case is presented by the house officer requesting the consultation; the reasons for asking aid are given by him, and the presentation includes his own pediatric-psychiatric appraisal. The psychiatric, psychometric and social service formulation is presented by the psychiatric "team," and discussion is initiated by the psychiatrist and continues informally, that of the practitioner being especially valuable, since it helps the psychiatric group to keep their feet on the ground and demonstrates to the younger pediatrician what is expected in private practice.

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Since time is not available in the monthly conferences for the consideration of every child referred for consultation, attempts are made to discuss each case with the referring physician in the informal manner described as soon as possible after an evaluation has been made. It has seemed important for good teaching practice to do this (even though it is time consuming) rather than merely to place a note in the patient's chart and rely on the pediatrician's chance reading of it. That the permanent record of the psychiatric appraisal has teaching possibilities in itself, however, has been recognized. Much time has been spent in its formulation so that the structure and content might be helpful in aiding the pediatrician not only to develop an organized method of personality study but also to modify the general pediatric anamnesis by incorporating a consideration of psychologic, educational and social factors in each case history. A discussion of the outline of the consultation record is given later in this paper, in the section on "Results."

The instruction of nurses has formed a part of the teaching program on the pediatric wards. This has been in part indirect—through contacts in daily ward rounds, when the care of the individual patient is considered by the house staff and the liaison physician—and in part direct—through individual conferences between the latter, the supervisors of nurses and the charge nurses to discuss matters relating to general and specific policies. For example, plans have been discussed for the management of intractable masturbation in isolated, restrained children who have become bored by the enforced inactivity of the hospital at a time when they feel able to be with their fellows, and for the management of pica in patients whose craving for objectionable materials might be directed toward more hygienic substances of the color and consistency of the prohibited articles. Lectures and demonstrations to groups of nurses on emotional and intellectual development and the psychologic aspects of nursing care and management of sick infants and children are given soon after these students take up their duties in the pediatric pavilions.

Senior medical students working as clinic clerks are included in the daily rounds of the house staff and participate in that teaching. In addition, they meet once a week with the liaison staff physician in informal discussion groups in the outpatient department, to consider problems arising from hospitalization. For example, such topics as the meaning of hospitalization to a child and his parents, the preparation of a child for hospital admission, the technic of hospital admission and reasons for bringing a child to a hospital are considered.

RESULTS

The results of the project are not easily measured, because too many intangible factors are present for one to determine accurately

whether the changing needs are being satisfactorily filled. Analysis by statistical methods is of limited value; a survey of the requests for consultation from 1939 to the present time provides some idea of the frequency with which extensive consultations have been requested but gives no information as to the number of requests for and the time spent in daily discussion with the staff members and in rounds of the wards and interviews with patients. A more important aid in the appraisal of results would seem to lie in a study of the type of requests for aid coming from the hospital personnel, to note the evolution of their interests and their changing roles and in a study of the changes made in the work-up and management of the hospitalized child. The results will be considered under the following subtitles: I. referral data, II. physical-emotional relationships, III. psychiatric-pediatric anamnesis, IV. social service aid, V. the role of the psychologist and VI. the training of the child psychiatrist.

I. Referral Data; Incidence and Types of Problems.—In a pediatric service of fifty-four beds with an average occupancy of 83 to 85 per cent there was an average referral for extensive psychiatric study of 12.4 per cent of all admissions. Of these, 80 per cent were from the age group of 2 to 15 years. At first some of the patients may have been referred as a means of "dumping," when they seemed to present no medical or organic factors, but for the most part there is now a genuine desire for aid in the diagnosis and treatment of the problems of the children as part of the pediatric work-up. The requests for the detailed psychiatric study are chiefly of children showing antisocial and asocial behavior (temper tantrums, delinquency and cruelty), difficulties of speech (stuttering, mutism and retardation of development), epilepsy and tics, mental retardation and learning difficulties and intractable bad habits, such as enuresis, anorexia, vomiting, pica, thumb sucking, sleep disturbances and body manipulation. Many of the problems are so complex that they require intensive psychotherapy, which is therefore best carried out in the psychiatric clinics. These severe disturbances are as a rule easily recognized by the younger pediatrician, and they fall into the category of the grossly pathologic, which is so stimulating to the young person in medicine.

For the maturing pediatrician, however, there is greater interest in the psychology of normal growth and development and in the prophylaxis of psychologic aberration. A large but undeterminable number of such cases are discussed in part during daily ward rounds and individual conferences, usually relative to some phase of development or of management; here the discussion is kept informative but general, lest the impression be given that specificity in management may safely follow cursory investigation of a problem. Discussions of this nature have

led to a consideration of many topics, prominent among which are the following: the influence of socioeconomic factors, the role of personal relationships (of parent to child, child to physician and parent to physician), the dynamics of psychologic and psychopathologic mechanisms, the psychologic concomitants of physical disease and medical treatment, psychosomatic medicine (the physical concomitants of emotional disturbances) and, finally, the preparation of a person for psychiatric care and an understanding of the various types of psychotherapy which are available. As opposed to the earlier requests for psychiatric consultation, which might be labeled diagnostic and therapeutic, the latter ones are chiefly characterized by prevention. The pediatrician feels increasingly able to name and classify the psychologic aberration; he understands better what psychiatric therapy consists in, but he is most concerned (as he is in other branches of pediatrics) with understanding basic principles of emotional, mental and physical growth, average and normal development at the various age group levels and the factors during infancy and childhood which mold the development of personality. Having heard so much, especially from the psychoanalytic groups, about the importance of good prenatal care, of acceptance of the newborn by his parents, of breast feeding and of casual (instead of rigid) toilet training, the pediatrician is ready to modify his ideas of pediatric care.

II. Physical-Emotional Relationships.—Observations of children admitted to the hospital have demonstrated that the average patient is emotionally disturbed by the experience and that practically every physical illness has some psychologic concomitants. These are usually of a nonspecific nature (except, of course, in such diseases as encephalitis, hypothyroidism and paresis) and range in type and severity from simple wonder and irritability at the new experience to fear, anxiety and even panic states, excessive motor activity or depression. These emotional states may in turn set up new physical reactions, such as fever, restlessness, enuresis, night terrors, anorexia, vomiting and diarrhea. These complications are disturbing to the physician, who is confronted with the task of treating the person as well as the disease. One of the great influences of psychiatry in medicine has been to emphasize psychosomatic relationships and to suggest technics of pediatric management which embrace psychologic as well as physical perspectives. Two areas of change resulting from this are (*a*) in the hospital care of patients and (*b*) in the understanding of interpersonal relationships.

(*a*) Changes Wrought in Hospital Care: Although the practice of pediatrics as a specialty is relatively young (and therefore theoretically more pliable) and has been greatly modified from time to time by schools of antithetic scientific thought, it is not to be expected or

desired that the influence of newer and "less scientific" psychologies would suddenly and drastically bring about further changes in the care of the child. Applying the scientific approach, pediatricians have carefully been making their own clinical observations of the emotional components of physical illness in order to verify and add to the observations made through more formal psychologic and psychiatric approaches and have then appraised their medical handling of the sick child. Even though the presence of psychologic blindspots and prejudices in the minds of observers interferes to some extent with the interpretation of observations, the pediatricians-in-training have in great measure used their findings to good advantage in modifying those procedures which seemed psychologically traumatic. For example, the erstwhile use of force in the handling of a child has stimulated much thought and some changes in hospital routine. Physical persuasion as a means of getting a child admitted to the hospital, of complying with isolation technic and of the administering of drugs, laboratory and surgical procedures was formerly accepted as necessary and time saving and unassociated with deleterious influence on the child; now it is used decreasingly by the physician who has become aware of its psychologic influence on the patient as well as of the widespread waste of time, of materials and of nervous energy of the hospital staff. The house officer who has resorted to force in dealing with an already anxious child has inevitably noticed that the added fear upsets the patient so much that his crying disturbs the routine of the ward patients, and the patient requires nurses to soothe him, when they are needed badly at other stations; that the usually well behaved youngster becomes suspicious, belligerent and revengeful (by disrupting hospital services) when he interprets his handling as undeserved punishment; that the diabetic child when coerced into complying with a little understood (by him) diabetic regimen reacts differently not only in his moods but also in his insulin-glucose metabolism. In contrast, patients are now given some preparation for new experiences. Attempts are made to explain the purpose of hospitalization and laboratory procedures; it is pointed out that hospitalization is not a punishment and that the patient will not be forgotten and left there. This information is given to the child not in the form of a preparatory speech or a didactic sermon but rather through the medium of answers to questions and of a discussion with the parents in the child's presence in a way which is informative but not productive of anxiety. The actions of the staff probably reassure the child and his parents more than any words could do; allowing a parent to accompany him to the ward and to visit him frequently usually dispels fears of parental rejection; talking to a child on his own level with consideration for his feelings, reducing the

period of isolation to a bacteriologic minimum, placing the patient in a ward with his age mates and keeping him occupied as much of the time as possible (commensurate with his physical state) will in the long run make him happy and "hospital abiding."

Another example of the changing management of a pediatric patient may be cited in the care of the nursing infant. Increased knowledge of nutrition and of infant feeding has shown that babies can be reared physically just as satisfactorily (and more conveniently) by feeding them cow's milk mixtures as by maternal feeding. Some "less modern" pediatricians continued to believe in the advantages of breast milk as food and developed methods of collecting and storing such milk supplies for feeding by bottle to the hospitalized infant. Mothers able to nurse their infants were barred from doing so by the isolation rules of the hospital. The importance of the nursing process itself to mother and child as a means of establishing a good basic emotional relationship between them was recognized long ago by physicians and mothers but discarded with the coming of the "bacteriologic era." The advantages of maternal nursing to the hospitalized infant are now again recognized and are encouraged whenever practicable, and the isolation technic is modified so that neither donor nor recipient is exposed to infectious diseases.

(*b*) Changes Wrought Which Lead to a Better Understanding of Interpersonal Relationships: As his knowledge of the psychologic development of children increases through guidance in observing and handling patients in the hospital, the pediatrician is acquiring an increasing ability to deal with people pedagogically and therapeutically. The physician-patient and physician-parent relationships are recognized as emotional as well as intellectual. The physician is less the adviser whose will must be enforced than the interpreter of behavior and the sympathetic nonjudicial counselor. For example, discussion with a parent about his child's masturbation is more than an intellectual appraisal of behavior in terms of total development; it embodies the relief of parental anxiety, shame and guilt. Then too, the pediatrician-in-training is less inclined to do something to the patient or to say something to reassure a person, in order to convince himself that he is treating the person; the art of listening sympathetically, for example, without venturing any interpretation or advice is more appreciated for its therapeutic possibilities as the physician experiments in his psychologic role in the care of the sick child and the parents.

Still another relationship to be considered at this point is that of the pediatrician to the psychiatrist in those cases requiring prolonged and intensive psychiatric care of child or parent. Both groups of specialists are beginning to realize that for such intensive therapy to be successful

some important requirements must be met and that these are fulfilled largely through the cooperation of both medical groups. Psychotherapy, in this instance, begins not when the referred patient consults the psychiatrist but rather earlier, through relationship with the pediatrician who understands the patient's needs and ways to help him. Before referral, there should be a period of preparation both of parents and child; the physician must be able to allay the distress, apprehension and misinformation of the average lay person about psychiatry. Referral must not be made by force, or even by mild urging, at a time when the patient is not ready for it. The physician, realizing the advantages of early psychiatric help, must not hasten it prematurely. The patient and his parents must realize the need, must want the help and should be made acquainted with its limitations as well as with its benefits. The exact technics vary and are not easily taught, but they are being acquired by the medical staff-in-training through learning more about their own feelings and about their relations to fellow human beings. Once formal psychiatric treatment is begun, the relationship between the patient and the pediatrician does not end; real support in the management not only of physical conditions but also of emotional ones which arise during psychiatric therapy is given by one specialist to the other. Consultations between the two not only help the patient but are educational and informative to both physicians.

III. The Psychiatric-Pediatric Anamnesis.—Another result of the influence of psychiatry in pediatrics is the change wrought in the medical history record. In the examples of changing methods in pediatric management previously cited, the important roles of the parents are defined in relation to the treatment of the patient. The pediatrician has long recognized that "treatment of the child includes treatment of the mother," though this could be better stated: "Study and care of the child includes consideration of other members of the family." The consideration of interpersonal family relationships should begin with the collection of historical material in the present illness of the anamnesis and should be carried through all situations related to the specific treatment of the patient. Analysis of the ordinary pediatric history record shows that this is not the plan usually followed. For various reasons, such as compactness and orderliness of record, this material is relegated to the compartment labeled "family history," with but a modicum of information about the family appearing here and practically none in the account of the present illness. This compartmental focusing in taking a history tends to bring about a lack of historical unity, and therefore a depersonalization, so that the medical record becomes a data sheet about a disease or pathologic process instead of an account of a person with a life history in which an

illness is but one important episode; the physician taking the history has difficulty in seeing the total person, while the informant loses that therapeutic release which comes through the recitation of his feelings about the sick person. At the New York Hospital, the structure of the psychiatric consultation record in the inpatient pediatric service has been so arranged as to present a historical account which will show the events of the patient's life in relief and in their proper relationship with other events and other people and still maintain a form which is not cumbersome, repetitious or impossible to incorporate into the general pediatric anamnesis. With time, the structure of the latter is assuming more of the arrangement and of the material of the consultation record. In general, the arrangement of the psychiatric-pediatric consultation record is as follows:

1. Statement of the Problem:—The problem as seen by the informants and by the referring physicians is stated.

2. Interview with Patient:—The interview with the patient includes an account of the present illness, into which is woven his reaction to it, to hospitalization and to separation from his parents and siblings. Topics of concern, his desire to get well and his personal history, with fears, fantasies, dreams and feelings toward family, schoolmates and agemates, are recorded as they are given spontaneously. Reactions to growing up and to events in the past history are also noted. Observations as to rapport, attitude and behavior, speech, mood, orientation and memory and apparent intelligence, as well as physical characteristics noted by inspection, are recorded.

3. Interview with Parents or Parent-Surrogates:—An account of the present illness with the reasons for coming to the hospital is given, much as the informants produce it, but the account is preceded by the physician's impression of the apparent reliability, intelligence and feelings of the informants as related to the patient. Information about the patient's personality and personal history is noted in relation to the present complaints.

4. Past History:—In the past history, the acceptance of the patient ante partum, birth and neonatal data, feeding, toilet training, development, illness, reactions to growing up, religion, discipline, sex development, good and bad habits and relation to siblings, fellows and school are described.

5. Family History:—The family history includes not only the customary statements about the ages and the health of parents and about familial diseases but also an elaboration of the child-parent relationship with a description of the psychologic environment of the family during infancy and childhood; the relationship of parents (or parent substitutes) to each other; their attitudes towards the child in his illnesses and in health and contrasted with their feelings towards other siblings, and the psychologic and somatic resemblances of the members of the family constellation.

6. Social History:—A social history giving the total family income, housing, facilities for recreation and for school and costs of rent and of food is also taken; this is amplified later by a social service survey.

Recording the historical approach of an anamnesis with such an associative sequence results in an organismic rather than an additive

total picture of the sick person. In taking such histories, the interviews are best fragmented, for this is less tiresome to the informants and to the physician; if succeeding interviews follow soon after the introductory one, the informants not only give additional valuable data but receive the therapeutic benefit of again being able to talk to the doctors about their worries or problems, and they are better able to accept the most difficult therapeutic regimen or unhappy prognosis.

The physician in practice has realized the importance of a good physician-patient and physician-parent relationship but has regretfully stated that training in suitable technics in this area has come only through hard experience once he has left the medical school and hospital. For this reason, adequate time should be available for the house staff members to have unhurried interviews with patients and parents after admission to the hospital, with follow-up consultations with medical and psychiatric colleagues in order to discuss the content and the diagnosis of the interviews.

IV. Social Service Aid.—The services of a psychiatric social worker have been available to the pediatric staff since soon after the beginning of child psychiatry in the pediatric outpatient department. When the scope of the project was extended to the inpatient unit in 1939 the social service increment changed similarly. The worker at first was used chiefly for ready reference to community resources and as an intermediary for the hospital and social agencies, but through contacts with the pediatricians on ward rounds and in individual case conferences she assumed a greater teaching role as well. Approaching the subject of care of the child as one of case study rather than as one of case disposal, the social worker has given the medical staff greater insight into the particular needs of the patient and has evaluated the structure and usefulness of specific social resources for supplying these needs. The limitations as well as the advantages of modifying environmental, school and socioeconomic factors which seem to affect childhood personality are stressed. This has resulted in a more efficient and more economical use of community resources, which at best are never too plentiful, and in a more realistic appreciation of their therapeutic aid. Being a participant in a case study and therapeutic program, the case worker has also demonstrated usefulness in acting as the person who may integrate the various medical endeavors. An acknowledged criticism of a large, busy clinic, where cases are referred freely from one specialist to another, is that the patient becomes confused by (what seems to him) the shifting emphasis on study, diagnosis and treatment of his physical and mental state. The social worker is able to steer the patient carefully from one consultant to another, to make the reasons for referral clear to him, to allay any misapprehensions arising as a result of it and, finally, to maneuver the patient to some one who

will integrate the conclusions and explain their meaning to him. When follow-up study and treatment are indicated, the worker is able to help the patient make arrangements for it; the busy physician is thus relieved of a time-consuming duty and is helped in his synthesis of the case. This delegation to the social worker of more work with the patient has resulted neither in a usurpation of the obligations, rights or privileges of either the patient or the physician nor in a dilution of pediatrics or psychiatry but rather in greater respect for a discipline that has aided medicine in a better understanding of the patient and, therefore, of its own therapeutic role.

V. The Role of the Psychologist.—The psychologist in the department of psychiatry has been readily available to the pediatric staff for the formal psychometric testing of patients admitted to the hospital. The reports of such studies, which become a part of the child's clinical record, carry, in addition, clinical impressions and interpretations by the liaison staff physician, who has observed the child in the hospital and has, when possible, interviewed the parents. Through conferences with the psychologist, the pediatrician has learned in detail the manner of giving and of interpreting the commonly used psychometric tests, such as those of Gesell, Cattell and Terman. He has been encouraged to give these tests to patients but has done so only in a limited way, partly because the press of hospital duties militated against their routine use or because he had little interest in giving the tests or little inclination to do so. On the other hand, he has been much interested in learning the correct interpretations and applications of the tests, and this has resulted in a better understanding of the meaning and relative importance of the concept of "intelligence" in the study and management of sick and healthy children. The large census of an active pediatric service includes many children who present problems of learning or behavior of a type suggesting mental retardation, and intelligence testing is indicated. Appraisal of the results, not alone in terms of the intelligence quotient of the patient but more in levels of intelligence under the terms of the testing situation, has been pointed out by the psychologist, who has also wisely counseled against the acceptance of the results as final, unchanging or unrelated to facts elicited by other studies. Retesting and reevaluation of "intelligence" under variable clinical circumstances have been suggested in appropriate cases, just as is done with any other laboratory test.

In this way the physician has seen that intelligence may be temporarily impaired in physical illness, such as long-standing cardiorenal disease, brain tumor or anemia, as well as in emotional disturbance, such as more or less severe anxiety states, and has seen that permanent

and progressive changes may follow cases of cerebral dysgenesis, lead encephalitis or endocrine dysfunction in cretinism or pituitary disease.

In cases of mental deficiency on a congenital or acquired basis the pediatrician is learning to rely on repeated psychometric testing for help in early diagnosis, prognosis and gage of treatment, instead of following haphazard methods, like playing hunches or waiting for the passage of time to bring changes. Prolonged observation of a patient satisfies parents that something is being done and helps them to accept the final diagnosis; such long term study clarifies in the mind of the physician the true meaning of the patient's intellectual state, and aids in the formulation of adequate social, educational and medical plans for future care.

VI. The Training of Psychiatrists in Pediatrics.—This paper has so far dealt only with the place of psychiatry in training and teaching pediatricians. Attention must also be given to the reciprocal role in these areas of the two specialties, since there can never be much distinction between teaching and learning. The patients of the Children's Clinic have been studied by Commonwealth Fund Fellows in Child Psychiatry not as psychiatric patients, but as sick and convalescent children. Ward rounds, discussions with the pediatric staff and observations of these children in the hospital setting have reviewed for these students the whole realm of physical illness and have helped them to a better integration of the concepts of emotional and of physical growth. For them, as for the pediatrician, these contacts have prevented compartmental thinking in terms of psychiatry or medicine and have emphasized the more truly monistic approach to the appraisal of human health and disease. It is logical that the preparation of the child psychiatrist no longer consists of training in psychiatry and psychology with a modicum of service in pediatrics. The newer approach to this specialty includes a greater contact with healthy and with physically sick infants and children and with the well trained pediatrician, who will demonstrate new developments in modern medicine which may contribute to his own special field as well.

CONCLUSIONS

The success of the psychiatric-pediatric inpatient service cannot easily be measured; too many intangibles are involved. Measurement by statistics alone is incomplete and is the least satisfactory determinant of value or of progress. It seems much more important to consider as primary that less tangible measure of success, namely, the amount of influence for good which has been accomplished in the training of physicians and hospital personnel and in the management of the hospitalized patient. In terms of the acceptance and the practice of psychiatric teaching (as heretofore the contributions of pathology, physics and

chemistry have been accepted) by the pediatrician-in-training and by the graduate practitioners, medical students and nurses the unit has seemed valuable and worthy of continuance and expansion. In no wise has there been a desire or attempt to convert pediatricians into psychiatrists; rather, efforts have been made to present relevant and usable technics which the physician can add to his pediatric armamentarium. Focus in this study has been on the physically sick child in the hospital setting, but this scope has to be widened to include such milieus as those of community, school and home, when the child is physically healthy. This is necessary because the normal growth and development of a child is broad and continuous and interspersed only periodically with illness. The pediatrician, and for that matter the psychiatrist as well, is better able to care for the sick child through knowing him as a healthy one. The episodes of illness are better evaluated when considered in relation to the other events of the child's life. The pediatrician recently trained is usually lacking in experience with the healthy infant and child and hence is not qualified for such an appraisal. Pediatric education of necessity, then, will in the future include more work in health projects of the nursery, elementary and secondary schools and in community interests, such as recreation and play activities, and especially in the most natural habitat of the child–the home. Observation of the children in these environments and work with persons, like parents and teachers, who supervise the activities will supply firsthand knowledge about a child's physical, psychologic and educational development, which can be used pedagogically with parents in the way of a preventive medicine as well as therapeutically through a better understanding of specific situations. The teaching program for pediatric house staff officers may be enhanced further by the establishment of regular seminar meetings for small groups of physicians, in order that there may be a sharing of experiences as well as guidance in training.

As time goes on, much that now appears like extracurricular experience appendant to the main body of pediatric training will either become dissociated from it because it is unessential or impractical or become assimilated into it by natural and vital growth. The degree to which the latter occurs and the character of the change wrought in child care in the future by pediatricians trained along the scheme presented herein will measure the validity of many of the hypotheses expressed in these papers.

Abstracts from Current Literature

Metabolism; Infant Feeding; Milk and Other Foods

Appraisal of the Nutritional Status of Children. Arild E. Hansen, New Orleans M. & S. J. **98**:261 (Dec.) 1945.

In these days of fads, fallacies and fancies in the nutritional field, it is refreshing to have available for perusal an article dealing with accurate figures and facts. In this paper the author outlines the known nutritional requirements for the child in calories, in fats, in proteins and in carbohydrates and in the accessory food factors, such as the vitamins and minerals, and presents them all in readily understandable tabular forms. Outlines are given for obtaining a satisfactory dietary history. Also presented are the known symptoms and signs of dietary deficiencies. Not the least valuable is an outline of a diet for the growing child which covers all known essential requirements. The article is recommended to all who wish to be truly factual in making out their patient's dietary programs.

Berkley, Beverly Hills, Calif.

Proteinemia, Normal and Pathologic, in Pediatrics. Antonio Sellek Azzi, Julio C. Mas Martin and Eladio de Castro, Bol. Soc. cubana de pediat. **17**:71 (March) 1945.

The authors report the results of studies of total blood protein, albumin and globulin in a series of normal children and in children with various pathologic conditions. They used the refractometric method of E. Reiss, except in cases of nephrosis and lipemia, when a colorimetric method was used. The normal levels of total protein in small children ranged from 5.56 Gm. per hundred cubic centimeters (minimum) to 7.11 Gm. (maximum). The albumin was 3.47 Gm. per hundred cubic centimeters (minimum) to 4.89 Gm. (maximum), and globulin 1.65 Gm. per hundred cubic centimeters (minimum) to 2.27 Gm. (maximum). There are tables of values in nutritional edema, other types of edema, vitamin B deficiency, nephrosis, nephritis, hepatic disease, parasitism, etc. In most of the conditions studied, hypoproteinemia was demonstrated.

Keith, Rochester, Minn.

Determination of the "Alkaline" Phosphatase of the Blood Plasma in One-Tenth Cubic Centimeter of Blood. G. van Veen and I. Denys, Nederl. tijdschr. v. geneesk. **86**:2918 (Nov. 21) 1942.

A method of determining the quantity of "alkaline" phosphatase in the plasma of 0.1 cc. of blood is described. This method is a combination of the micromethod of Raoul and Vinet and that of King and Armstrong.

van Creveld, Amsterdam, Netherlands.

Physiologic Values of Metabolism. J. Jongbloed and B. W. Grutterink, Nederl. tijdschr. v. geneesk. **87**:76 (Jan. 9) 1943.

Every third or fourth day for about eight months the metabolism of 2 men was determined with the apparatus indicated by Noyons, in order to determine the physiologic spreading. The total number of measurements amounted to sixty-one and sixty-five respectively. Expressed in terms of the "normal" value according to Harris and Benedict, an average value was found of 103.3 plus or minus, 4.3 per cent and 86.3 plus or minus 3.6 per cent. From this the conclusion can be drawn that with a careful technic, with a deviation of plus or minus 10 per cent of the real normal value the border of the physiologic value is reached, and that

one should already be on the alert when there is a deviation of plus or minus 5 per cent. However, as the calculated "normal" value can easily be several degrees higher or lower than the "real" normal value, these percentages of 10 and 5 are, in practice, only to be regarded as an average, where the deviation from the calculated normal value is concerned.

VAN CREVELD, Amsterdam, Netherlands.

Newborn

KERNICTERUS: NEUROLOGICAL SEQUELAE OF ERYTHROBLASTOSIS FOETALIS. JACK M. DOCTER, J. Pediat. **27**:327 (Oct.) 1945.

Pathologically kernicterus is a pigmentation and degeneration of the nerve cells of the brain, particularly the basal ganglions. Clinically kernicterus is the manifestation of this degeneration as seen in the living patient, that is, extrapyramidal spasticity, convulsions, delayed motor functions, incoordination, chorea, athetosis, ataxia and retardation of mental development. A review of the literature reveals that this condition originates only in newborn infants with severe hemolytic jaundice and anemia. There are no case reports of kernicterus occurring solely with an obstructive jaundice, or at any time during life other than in the newborn period. It is almost universally associated with erythroblastosis fetalis.

Recent advances in the study of erythroblastosis fetalis and of the Rh factor resulting in an increased survival rate of victims of this disease have made of increasing significance the relationship of neurologic sequelae to severe neonatal jaundice. In a study of 34 cases of jaundice of the newborn at the Children's Memorial Hospital, 20 were found to be due to erythroblastosis fetalis and 15 had some of the manifestations of kernicterus.

Three of the cases showing some of the manifestations of kernicterus were not in the group of erythroblastosis fetalis, and there were other adequate explanations for the neurologic signs, that is, neonatal cyanosis and anoxemia, evidence of birth injury and cretinism. The remaining 12 cases of kernicterus were all in the group of 20 cases of erythroblastosis fetalis. This is 55 per cent, a figure larger than that previously reported in the literature. None of the cases in this series was associated with obstructive jaundice.

AUTHOR'S ABSTRACT.

ERYTHROBLASTOSIS FETALIS. HARRY R. LITCHFIELD, J. Pediat. **27**:353 (Oct.) 1945.

The article "Erythroblastosis Fetalis" reviews the incidence of the disease and the many theories regarding isoimmunization. The clinical aspects of the paper are taken up with concrete cases together with findings at necropsy. The treatment is outlined in detail.

Erythroblastosis fetalis is the broad clinical picture in which are included several clinical entities: (1) anemia of the newborn, (2) icterus gravis neonatorum and (3) hydrops fetalis.

Clinically, hydrops fetalis is the severest form of erythroblastosis. A stillborn infant or death after feeble respiration is the rule. The longest life period recorded is six days. The infant presents a waxy skin with multiple zones of cutaneous hemorrhage. Edema is pronounced. Jaundice is occasionally noted. The face is enlarged and swollen, the neck is short, and the abdomen is markedly distended. The latter condition results from the presence of free fluid in the abdominal cavity and from enlargement of the liver and spleen, which are felt for varying distances below the costal arch.

The diagnosis of hydrops fetalis is easily established at birth by the clinical appearance of the infant and is confirmed by study of smears made from cord blood. Even before delivery, an amber amniotic fluid directs suspicion. Intrauterine diagnosis can be made by roentgen rays, as first shown by Hellman and Irving. In the roentgenogram the subcutaneous tissues are definitely thickened and show considerable density. A corona surrounds the bones of the skull due to pronounced edema of the scalp.

In January 1940 Landsteiner and Wiener, continuing their researches on rabbit immune serums produced with blood of rhesus monkeys (which had previously been found able to react with human bloods that contain the agglutinogen M) found that another individual property of human blood, which they designated Rh, could be detected with some of these serums. When anti-Rh serums became available, these were used by Levine in tests on the patient reported by himself and Stetson in 1939, and proof was obtained that the factor involved was Rh and that the material agglutinin was anti-Rh.

In clinical medicine the Rh types serve to explain a certain number of the hitherto puzzling instances of hemolytic transfusion reactions when both the father and the mother had Rh positive blood. In the cases in which isoimmunization has occurred between different Rh blood types, the use of Rh negative blood is indicated for the same reason that group O blood can be used for persons of group A, B and AB in ordinary blood transfusions.

In a review of 3,885 infants delivered at the Beth-El Hospital, Brooklyn, N. Y., for a period of eighteen months there were 94 stillborn, and of the infants whose death was unexplained (stillborn), there were 46 boys and 27 girls. In 40 of the newborn erythroblastosis or anemia or jaundice developed, and of these 26 were boys and 14 were girls. Eleven of the infants with erythroblastosis died; of these, 10 were boys and only 1 was a girl. In 1 case, in which there was no necropsy, the sex could not be determined. The blood of the mothers of these infants was all Rh negative except in 1 instance, in which the blood was positive. Routine determinations of the Rh factors in all obstetric cases were performed. In the first 500 determinations they found 66 women with Rh negative blood, an incidence of 13.2 per cent. According to these statistics, it was found that boys are more prone to have erythroblastosis in the ratio of 3 to 1; and in the fatal cases boys were more numerous in the ratio of 5 to 1.

AUTHOR'S ABSTRACT.

APPENDICITIS IN THE NEWBORN—REPORT ON CASE 16 DAYS OLD. W. ETHERINGTON-WILSON, Proc. Roy. Soc. Med. **38**:186 (March) 1945.

An account is given of appendicitis in infancy. Early postnatal appendicitis is rare. It is extremely liable to be fatal in patients under 4 weeks of age but less liable to be so as age advances. A case of appendicitis, the symptoms beginning on the fourteenth day, with an operation on the sixteenth day, is recorded by the author.

WILLIAMSON, New Orleans.

TETANUS NEONATORUM WITH UNUSUAL COMPLICATIONS. L. PALBY, Ann. pædiat. **165**:223 (Oct.) 1945.

A case of tetanus neonatorum with umbilical infection complicated by prolapse of the rectum is reported. The diagnosis was confirmed at autopsy.

GRULEE, Evanston, Ill.

Acute Contagious Diseases

DIPHTHERIA IN AN "ADEQUATELY" IMMUNIZED COMMUNITY. BERWYN F. MATTISON, New York State J. Med. **44**:2138 (Oct. 11) 1944.

An epidemic of 28 cases of diphtheria in a city (Kingston, N. Y.) of 28,589 population is reported. Previous studies in this city had shown a low carrier rate of 0.03 per cent and a decreasing natural immunity. There was a history of previous immunization for 75 per cent of the children of school age and 44 per cent of the preschool group. The disease occurred predominantly in children of school age, all of whom had not been protected or had been given less than the recommended dose of toxoid or had been immunized five or more years earlier and had had no subsequent restimulation. It is suggested that the levels of artificial immunization formerly adequate to protect a community may no longer suffice.

Higher levels may be maintained by higher preschool protection, reimmunization of all children on entrance to school and administration of complete courses for every person immunized.

DAVIS, Rochester, N. Y.

THE FIRST EPIDEMIC OUTBREAK OF POLIOMYELITIS IN QUITO. CARLOS ANDRADE MARIN, Rev. chilena de pediat. **16**:177 (March) 1945.

This is a review of epidemiologic, clinical and therapeutic observations in the first major outbreak of poliomyelitis in Quito, Ecuador. Of 57 patients with paralysis studied, 7 died and 7 recovered completely; of the remaining 43, about half tended to have notable regression of the paralysis. The Kenny method, thiamine, neostigmine and occasional epidural injections of solution of strychnine were employed. Enthusiasm for the use of neostigmine was evidenced.

PLATOU, New Orleans.

CHEMOTHERAPY IN DIPHTHERIA. J. VAN LOOKEREN CAMPAGNE and F. J. WESTENBERG, Nederl. tijdschr. v. geneesk. **88**:14 (Jan. 18) 1944.

Between January 1942 and September 1943 91 patients up to the age of 10 with diphtheria were treated with sulfathiazole and serum, and 113 patients were treated with serum alone. The definite impression was obtained that the administration of sulfathiazole had no influence on the course of the disease. However, the time between the entrance of the patient into the hospital and the first negative throat culture was on an average somewhat shorter for the group treated with sulfathiazole than for the other group of children.

VAN CREVELD, Amsterdam, Netherlands.

Acute Infectious Diseases

SALICYLATE THERAPY IN ACUTE RHEUMATIC FEVER. RENÉ WÉGRIA and KATHARINE SMULL, J. A. M. A. **129**:485 (Oct. 13) 1945.

Adequate salicylate therapy was given to 21 patients with rheumatic fever. This consisted of the maintenance of blood salicylate levels between 350 and 500 micrograms per cubic centimeter until the sedimentation rate had been below 20 for two weeks. The dosage necessary to maintain this level was 0.9 to 1.8 Gm. every four hours. It was found more satisfactory to initiate therapy by doubling this dosage for the first twelve hours rather than by giving salicylates intravenously. Sodium salicylate with enteric coating was used.

Tinnitus commonly developed at blood salicylate levels of 200 micrograms per cubic centimeter. Deafness, nausea and transient albuminuria were also found. Serious toxic symptoms occurred in some patients when blood levels went above 500 micrograms per cubic centimeter.

The course of the disease as measured by the fall in sedimentation rate was compared in the treated group and in a control group of 19 patients who had small doses of salicylates or in whom the optimal levels were not maintained. The course of the disease in the 2 groups was similar. Results in the treated group might have been better had treatment been begun earlier, only 5 receiving therapy in the first week of their having the disease.

BAIRD, Wauwatosa, Wis.

SALICYLATE THERAPY IN RHEUMATIC FEVER IN CHILDREN. LEO M. TARAN and MARTIN H. JACOBS, J. Pediat. **27**:59 (July) 1945.

It is generally agreed by clinicians that the favorable effects of salicylates on the course of acute rheumatic polyarthritis is striking and often dramatic enough to give the impression that salicylates may have a specific therapeutic effect on

the rheumatic process. To date no evidence has been presented to show that other manifestations of rheumatic disease such as chorea, carditis, rheumatic nodules and other cutaneous manifestations are favorably modified by salicylate therapy. The contention of Coburn that massive salicylate therapy may modify "the sterile inflammatory reaction which occurs during activity of the rheumatic process and inhibit the development of cardiac disease" has once more opened the question of the specificity of salicylates as therapeutic agents for rheumatic disease.

In this paper observations are presented on the effect of massive doses of sodium salicylate on the course of rheumatic polyarthritis and acute carditis in children 6 to 14 years of age. The intravenous and oral routes of administration are compared in regard to blood plasma levels, effects on rheumatic activity and the possible untoward effects or hazards.

The observations suggest that large doses of salicylates sufficient to raise the plasma salicylate level to 350 to 450 micrograms per cubic centimeter produce prompt and effective subsidence of all clinical and laboratory evidence of rheumatic activity in children having rheumatic polyarthritis. The oral route of administration is as effective as the intravenous.

The authors' observations further suggest that massive doses of salicylates in acute rheumatic carditis are equally effective in promptly suppressing all clinical and laboratory evidence of rheumatic activity. The intravenous route of administration in this group of cases seems to be hazardous.

It is further observed that the usual small doses of salicylates have no therapeutic value in rheumatic carditis in children.

While it cannot be definitely stated from the authors' observations that massive salicylate therapy unequivocally suppresses the rheumatic process and prevents the stigmas of heart disease, it is clear that this form of treatment makes the patient symptom free. It is not, however, clear whether this form of therapy simply suppresses the symptoms or indeed breaks the chain of processes operative in rheumatic activity.

The experience with intravenous use of massive salicylate therapy indicates clearly that more fundamental data must be presented to show the effect of a rapid rise of plasma salicylate level on hepatic metabolism and its possible injurious effects before the method is proposed for use generally.

AUTHORS' ABSTRACT.

RHEUMATIC HEART DISEASE WITH ASSOCIATED MENINGOENCEPHALITIS. R. H. HIGH and E. E. AEGERTER, J. Pediat. **27**:343 (Oct.) 1945.

Rheumatic infection affects other tissues than the heart and joints in its generalized involvement of the fibrous tissues and the valvular bed.

Recently the authors observed the clinical manifestations of meningitis in a child with chronic rheumatic carditis. The findings at necropsy revealed no changes in the central nervous system other than ones similar to the rheumatic type of perivascular lesion which were widely distributed in the heart and lungs.

The child, a Negro boy 12 years of age, was admitted to Temple University Hospital with headache, vomiting, pain in the neck and the back and drowsiness. For the past seven years he had had recurrent attacks of rheumatic fever.

A physical examination revealed typical signs of meningeal irritations and also of rheumatic heart disease.

The cerebrospinal fluid was purulent, but no organisms were recovered from 7 specimens.

He was treated with sulfadiazine and appeared to be improving, in fact almost well, when he suddenly died on the fourteenth day of his illness.

The important findings at necropsy were the changes typical of chronic and also active rheumatic infection of the heart, congestion of the lungs, and herniation of the cerebellum through the foramen magnum.

Microscopic sections of the heart and lungs showed the characteristic histologic changes of rheumatic fever. Sections from the brain and the meninges showed

perivascular lymphocytic infiltration with occasional large cells closely resembling those seen in the Aschoff body. The form of these cellular aggregates was similar to, though not identical with, that of the Aschoff body.

Because of the similar cellular reaction in the brain and the meninges, closely resembling thé typical changes of rheumatic infection found in the heart and lungs, it seemed warranted to assume that the cerebral and meningeal lesions were produced by the same etiologic agent.

AUTHOR'S ABSTRACT.

TOXOPLASMOSIS HOMINIS. S. L. BRUG and J. J. T. Vos, Nederl. tijdschr. v. geneesk. **86**:2956 (Nov. 28) 1942.

The authors review the most recent literature on human toxoplasmosis. Further anatomic and parasitologic details are given concerning a case observed in Groningen (northern part of the Netherlands). In this case the sections of the brain contained parasites which obviously were multiplying by schizogony.

VAN CREVELD, Amsterdam, Netherlands.

TRANSFER OF TYPHOID BY MEANS OF CHEESE. G. D. HEMMES, Nederl. tijdschr. v. geneesk. **86**:3159 (Dec. 12) 1942.

Eight persons, all of whom had eaten from the same cheese, became ill with typhoid. Forty days after the making of this cheese the typhoid bacilli still could be cultured from it.

VAN CREVELD, Amsterdam, Netherlands.

Chronic Infectious Diseases

A STUDY OF THE TYPE OF LESION OF TUBERCULOSIS IN THE COURSE OF REINFECTION IN THE CHILD. MIGUEL A. VALIENTE, CARLOS AMADOR and PEDPO G. HOYOS, Bol. Soc. cubana de pediat. **17**:131 (April) 1945.

The authors studied 2,100 patients with active tuberculous lesions in the Calmette Dispensary, Habana, Cuba. They discuss particularly the secondary infiltrations, as established by Redeker, as well as the tertiary or adult type of reaction. They sum up their observations as follows:

The secondary infiltration, called also "postprimary," is the most frequent form of the infection in infancy. The tertiary lesions of the adult type were almost never encountered in children and observed with any frequency only in puberty and adolescence.

In this study of 5,000 clinical histories and roentgenograms of children with positive reactions to the Mantoux test and of a total of 2,100 patients with active tuberculosis, some 300 patients (14 per cent) showed secondary infiltration, and only 41 (2 per cent) tertiary lesions.

The clinical symptoms which point to reinfection of a secondary type are varied. Only the positive reaction to the tuberculin test and the roentgenograms give any evidence of the pulmonary process. Other insidious symptoms are slight fever, asthenia, pallor, anorexia, loss of weight with cough and slight pulmonary signs. A few patients have high fever and signs of pulmonary consolidation. Hemoptysis was not observed.

The seat of the lesion is usually perihilar with a distinct roentgenographic picture. It may have a triangular form (Sluka) or the appearance of a transverse band or may be a mass which invades one or more lobules.

The course of these infiltrations is benign in almost all cases, and the condition clears up in one or two years. In rare cases caseation has occurred (secondary phthisis) with cavity formation.

Other secondary manifestations occur such as pleurisy, peripheral adenitis, phlyctenular conjunctivitis, tuberculous peritonitis and granuloma.

The tertiary (adult type) infiltration is established by a new infection which can appear in a lung free of lesions or in an area previously infected.

The clinical symptoms are usually indefinite in the early stages. Only in one third of the cases are there acute symptoms, for example, fever and respiratory involvement, almost always nonspecific.

If the symptoms are insidious at the beginning in the majority of cases, this is not so when the infiltration begins to break down. There are then intense symptoms, elevated temperature, cough, fatigue, anorexia, rapid loss of weight, pain in the chest and bloody sputum. On physical examination there are stertorous rales which soon become the type heard with cavitation.

The site of the lesion at the beginning is frequently infraclavicular although it can settle in other regions of the lung. The roentgenographic aspect is that of a round or oval shadow of rather thin density about the size of a coin of 10 or 20 centavos with a great deal of density at the edges.

The evolution of the tertiary infiltration is generally malignant, producing progressive clinical stages to caseation, softening, cavitation and dissemination of the lesion. Without doubt at any moment the process can regress toward cure or remain stationary for a considerable time.

A number of cases of osteoarticular tuberculosis which, according to many authors, constitutes tertiary lesions, have been observed in children who were affected or not affected with the pulmonary process. They observed 1 case of laryngeal tuberculosis and 1 other of renal tuberculosis, both connected with ulcerocaseous tuberculosis.

The secondary infiltrations, as much as the tertiary infiltrations, are of the type of reinfection recognized as being of exogenous-aerogenous origin. The possibility that the reinfection can have also an endogenous origin is admitted by all authors, giving it an origin from some reservoir still active or from some other infected organ. But in either case, it is to be admitted that reinfection is produced only when certain favorable circumstances exist, e. g., the kind of life, faulty hygiene, food deficiencies and intercurrent infections.

The bases of the diagnosis of these infiltrations of reinfection are the possibility of contagion, the physical examination, the tuberculin test, the erythrosedimentation rate, the hemogram, the search for the tubercle bacillus in the sputum and the roentgenographic examination. Of all these the most important are the history, the tuberculin test, the appearance of bacilli and the roentgenogram.

The differential diagnosis between secondary infiltrations and the primary infection is difficult when one does not know the history of the child or his tuberculin test has not been previously made. At times there are in the roentgenogram the remains of primary infection with the secondary infection around it, but there is no doubt that in a considerable number of cases it is impossible to determine with certainty whether a primary infection somewhat delayed is being treated or an early secondary lesion.

The differential diagnosis is easier between the tertiary infiltrations and the primosecondary. The greater age of the child, the circumstances of his early life in tuberculous surroundings, the knowledge of a positive reaction to a tuberculin test in previous years, the site of a new lesion, the primary calcified complex and the rapid evolution of the lesion (generally to caseation), with the early finding of the tubercle bacilli in the sputum, are all valuable data. In some cases the authors met with considerable difficulty in establishing a definite diagnosis between primosecondary and tertiary disease. At times only the study of the anatomic lesions at necropsy could clear this up.

KEITH, Rochester, Minn.

Diseases of Blood, Heart and Blood Vessels and Spleen

RHEUMATIC HEART DISEASE. IWAO UYEDA, New Orleans M. & S. J. **98**:271 (Dec.) 1945.

The author presents a statistical study of 167 proved cases of rheumatic heart disease found in a series of 12,357 routine necropsies. This constituted an incidence of 1.35 per cent, and approaches very closely the figures obtained by similar studies

in Northern hospitals. Rheumatic heart disease was the cause of death in 63 per cent of the cases and incidental in 24 per cent. In 94 per cent of the cases the mitral valve was involved, and the mitral and aortic in 25 per cent. Only 1 instance of pulmonary valvular involvement was found. BERKLEY, Beverly Hills, Calif.

FAMILIAL HEPATOSPLENOMEGALY. A. J. M. LOHMAN, Nederl. tijdschr. v. geneesk. **88**:99 (Jan. 29-Feb. 5) 1944.

Four out of 9 children from healthy parents had a distinct enlargement of the liver and the spleen. Six children showed a positive reaction to the Takata test, 1 child had ascites and jaundice, 1 only ascites, and 1 only jaundice. In 4 children the total cholesterol content of the serum was very low. The child with ascites and jaundice, a boy of 9 years, died after an illness of some weeks. At the necropsy classic Laënnec cirrhosis with fibroadenoma of the spleen was found. For the child with ascites, a girl of 10 years, the diagnosis of Laënnec's cirrhosis also was made. In the third child, a girl of 9 years, it was not possible to differentiate clinically with certainty between acute hemolytic anemia (Lederer) and congenital hemolytic jaundice. After biopsy of the liver and of the extirpated spleen, the diagnosis of hemolytic jaundice could be rejected; here also a cirrhotic process was found.

As regards the cause of this familial hepatosplenomegaly, stress is laid on the regular use of mustard by all children from the age of 1 year on. Only the child who only rarely made use of mustard had no changes in the liver and spleen; moreover, her functional tests were normal. It is known that allyl compounds, present in mustard, give rise to damage of the liver and the spleen, especially in young children.

Accepting mustard as the causal factor of the damage of liver and spleen, it is only peculiar that in the first case icterus predominated, in the second case ascites, and in the third case hemolysis. VAN CREVELD, Amsterdam, Netherlands.

Diseases of Lungs, Pleura and Mediastinum

THE TREATMENT OF PNEUMOCOCCIC PNEUMONIA WITH ORALLY ADMINISTERED PENICILLIN. PAUL A. BUNN, WALSH MCDERMOTT, SUSAN J. HADLEY and ANNE C. CARTER, J. A. M. A. **129**:320 (Sept. 29) 1945.

Forty-five patients with pneumococcic pneumonia, between the ages of 15 and 89 years, were treated with orally administered penicillin. The dosage arrived at was 750,000 units the first day and 400,000 to 600,000 on subsequent days (given as 50,000 units every two hours) with omission of the night doses twenty-four to thirty-six hours after the crisis.

Clinical results were good. There was 1 death and 1 serious complication. Three patients were changed from oral to intramuscular administration without change in rapidity of improvement. Moderate abdominal distention did not interfere with efficacy of treatment, but pronounced abdominal distention is a contraindication to oral administration. There were no untoward effects except for mild urticaria in 1 patient.

Results obtained with the use of powdered penicillin in water or in capsules were as good as those with the use of penicillin in oil. Blood levels in acutely ill patients were at least as high as those obtained from the same dose of penicillin in normal subjects.

Therapy should be continued for seven or more days to diminish the possibility of relapse. BAIRD, Wauwatosa, Wis.

PNEUMOPATHIES DUE TO HYDROCARBONS. JULIO MENEGHELLO, JULIO GUASCH and RAUL EBERHARD, Rev. chilena de pediat. **16**:293 (April) 1945.

Following a brief review of pertinent literature, the authors analyzed 12 cases of accidental poisoning of children between the ages of 5 months and 4 years.

Estimates of amounts ingested varied from 20 to 200 Gm. Early symptoms were alarming: cough, pallor, suffocation and cyanosis. Loss of consciousness occurred in 3 cases and a convulsion in 1. Excessive salivation, vomiting and alterations in cardiac and respiratory rhythm were also observed. These changes were assumed to be due to the action of the poison on the respiratory center, lasted only a few hours and had almost completely disappeared by the next day. In half the cases there was fever, beginning within nine hours and continuing for two days; the highest recorded temperature was 38 C. (100.4 F.). Beyond this time the cases were "silent," with basilar pulmonary infiltrations noted by roentgenogram only. In serial observations, such evidences appeared within three hours and cleared at eight to ten and eighteen days in 3 cases which could be followed. In addition to gastric lavage, sedation, inhalation of oxygen and carbon dioxide and chemotherapy were used to combat complications.

PLATOU, New Orleans.

Diseases of the Gastrointestinal Tract, Liver and Peritoneum

THE USE OF HUMAN IMMUNE SERUM GLOBULIN (GAMMA GLOBULIN) IN INFECTIOUS (EPIDEMIC) HEPATITIS IN THE MEDITERRANEAN THEATRE OF OPERATIONS: II. STUDIES ON TREATMENT IN AN EPIDEMIC OF INFECTIOUS HEPATITIS. SYDNEY S. GELLIS, JOSEPH STOKES JR., H. WALTER FORSTER JR., GEORGE M. BROTHER and WILLIAM M. HALL, J. A. M. A. **128**:1158 (Aug. 18) 1945.

In a series of 278 cases human immune serum globulin, 0.3 cc. per pound (0.5 Kg.) of body weight, was administered intramuscularly to alternate patients with the earliest symptoms suggestive of infectious (epidemic) hepatitis. No evidence was obtained from the patients studied in favor of an attenuating effect of human immune serum globulin when administered early in the course of the disease.

BAIRD, Wauwatosa, Wis.

Nervous Diseases

PENICILLIN IN THE TREATMENT OF PNEUMOCOCCIC MENINGITIS: A STUDY OF 67 CONSECUTIVE CASES. EMANUEL APPELBAUM and JACK NELSON, J. A. M. A. **128**:778 (July 14) 1945.

Sixty-seven patients with pneumococcic meningitis were treated with penicillin administered intrathecally, with total doses varying from 10,000 units to 700,000 units. In a few cases intracisternal, intraventricular or subdural administration was employed. All but 3 of the patients received additional penicillin intramuscularly or intravenously. Treatment with sulfonamide compounds, usually sulfadiazine, was given prior to or in combination with the penicillin treatment in almost all cases. The mortality rate was 61 per cent. Factors adding to the difficulty of successful treatment are the presence of primary foci of infection, the presence of bacteremia and the occurrence of the disease in fulminating form.

BAIRD, Wauwatosa, Wis.

MENINGITIS DUE TO SALMONELLA PANAMA. WILLIAM H. WOOD JR., FRANK H. MAYFIELD and ARTHUR W. FRISCH, J. A. M. A. **128**:868 (July 21) 1945.

Meningitis due to Salmonella Panama was observed in 2 infants three weeks of age who were born within four days of each other at the same hospital. The source of infection is believed to have been a carrier of this organism who worked in the hospital milk laboratory. The period of exposure ranged from five to thirteen days. The onset of symptoms occurred in seventeen to twenty-three days.

Sulfadiazine was used for periods ranging from fifteen to thirty-four days. One patient survived with this treatment, but the other died of internal hydrocephalus due to an inflammatory obstruction, though the cerebrospinal fluid remained sterile.

The authors recommend routine cultures of stools from all hospital attendants who come in contact with infants and debilitated patients.

BAIRD, Wauwatosa, Wis.

HUMAN ENCEPHALITIS IN THE YAKIMA VALLEY, WASHINGTON, 1942, WITH FORTY-NINE VIRUS ISOLATIONS (WESTERN EQUINE AND ST. LOUIS TYPES) FROM MOSQUITOES. W. McD. HAMMON, W. C. REEVES, S. R. BENNER and BERNARD BROOKMAN, J. A. M. A. **128**:1133 (Aug. 18) 1945.

A study of 28 cases of encephalitis in patients ranging from 11 days to 71 years of age in the fourth annual epidemic of the Yakima valley area revealed 11 cases in which increased titer of antibodies developed to either the western equine or the St. Louis virus or both, and 10 in which increased antibody titers failed to develop. The remaining cases were not studied completely. Two patients died. Twenty-six recovered, some with residual neurologic conditions.

The activity of the Culex tarsalis mosquito corresponded to the epidemic wave. The rate of infection in these mosquitoes was as high as 1 in 210. Forty-one strains of western equine and 4 strains of St. Louis virus were isolated from them. Culex pipiens was found to be infected with both types of virus but to transmit only the St. Louis virus, of which it is a proved natural vector. Culiseta inornata was found to be infected with and capable of transmitting the western equine virus, of which it is, therefore, a proved natural vector. Thirty to 50 per cent of the chickens in the region were found infected with western equine virus but very few with the St. Louis type.

Psychology and Psychiatry

INFANT SPEECH SOUNDS AND INTELLIGENCE. ORVIS C. IRWIN and HAN PIAO CHEN, J. Speech Disorders **10**:293, 1945.

In a statistical analysis of Kuhlman test scores and the Chen index of speech development of 19 children from 1 to 6 months of age, 22 from 7 to 12 months, 32 from 13 to 18 months and 18 from 19 to 24 months, it was found that speech sound development for the first two years of life is independent of intelligence test scores. Chen's differential method of scoring the elements of premeaningful infant speech may be considered another useful index in estimating the general development of infants.

PALMER, Wichita, Kan.

ANOREXIA IN CHILDHOOD. N. VEZINA, Union méd. du Canada **74**:140 (Feb.) 1945.

In the effort to achieve a perfect diet through research into nutritional requirements, physicians and parents have lost sight of the fact that eating is a physiologic function influenced by sensory contacts with food. This function may be modified by emotional factors. A large portion of feeding difficulties are caused by the negativistic reactions of the older infant. Development of a normal appetite requires a favorable and harmonious atmosphere. The complex process of eating develops from the suckling stage through the chewing stage to self feeding at a different rate in various infants, according to the speed of maturation of the neuromuscular mechanism. An artificially shortened suckling stage may result in substitution phenomena, such as thumb sucking.

DAFFINEE, Melrose, Mass.

POLIOMYELITIC CHANGES IN MULTINUCLEATED NEURONS, WITH SPECIAL REFERENCE TO THE SITE OF ACTION OF VIRUS IN THE CELL. DAVID BODIAN, Bull. Johns Hopkins Hosp. **77**:49 (July) 1945.

Numerous multinucleated neurons were found in the brain, spinal cord and spinal ganglions of an adolescent rhesus monkey, which had been killed during the

acute stage of poliomyelitis. Many anterior horn cells containing two to six nuclei had poliomyelitic degenerative changes characteristic of those seen in ordinary neurons. A striking observation was that the nuclei in any single multinucleated cell were invariably identical or almost identical in appearance, regardless of the degree of poliomyelitic change. The interpretation of this phenomenon led to the hypothesis that the primary action of virus is in the cytoplasm and that nuclear degeneration in poliomyelitis, including the formation of intranuclear inclusion bodies, may reflect the general degradation of cell functions rather than direct virus action.

AUTHOR'S ABSTRACT.

THE DIETARY ROLE OF HISTIDINE IN THE IMMATURE AND ADULT RAT. ANTHONY A. ALBANESE and JANE E. FRANKSTON, Bull. Johns Hopkins Hosp. **77**:61 (July) 1945.

Evidence as to the essential role of histidine in the diet of the rat is conflicting. Rats were given a control diet and a histidine-deficient diet, in which the protein fraction was a mixture of nineteen crystalline amino acids, for periods of four weeks. The growth curves indicate that histidine is required for the growth of the young rat and for the maintenance of weight in the adult rat.

LYTTLE, Los Angeles.

Skin Diseases; Allergy

THE ALLERGIC CHILD IN CAMP. JEROME GLASER, J. Pediat. **27**:75 (July) 1945.

An important consideration in the treatment of any chronic disease, and this is especially true in childhood, is an attempt to prevent the patient from developing a sense of invalidism. The more a child can enjoy activities common to other children of his age, the happier and healthier he will be. Camps especially for diabetic children are highly successful and have contributed to knowledge of diabetes in childhood. Camps especially for children suffering from allergic disease have not as yet been established, but with the advances which the field of allergy is making as a specialty, it is now perhaps time to consider the desirability for organizing such camps. Meantime all pediatricians and allergists every summer are confronted with the problem of what to do about their young patients who wish to go to camp.

A primary consideration in deciding to which camp an allergic child is to be sent is whether there is a resident physician, or at least a resident nurse, with a physician readily available on short notice. A child on a highly restricted diet should not be sent to camp, even if the diet is one which requires the elimination of particular foods which can easily be omitted, unless the child is known to be very cooperative. Every child should have a thorough physical examination before being sent to camp. In the case of the allergic child, in addition to the usual prophylaxis which all children should have, such as smallpox vaccination, diphtheria immunization and hypoimmunization against pertussis, it is particularly important that an allergic child be immunized against tetanus by means of tetanus toxoid. The attention of the camp physician should be particularly called to this so that the child if injured will not needlessly be given tetanus antitoxin. If for some reason the child is not actively immunized against tetanus, the camp physician should be instructed to use not horse tetanus antitoxin but bovine tetanus antitoxin except for those children known to be sensitive to beef or milk. The indication for inoculation against typhoid is the same for the allergic child as for the nonallergic child and depends on the circumstances under which the camp is conducted.

If the child suffers from pollinosis, it is advisable to send the child to a pollen-free area if possible. The child should remain there until the pollen season is well over, even though this may require omitting the first week or two of school. All injection treatments which are given at home should be given in camp, but

careful directions should be given the camp physician so that they will be properly administered.

The child should take to camp an adequate supply of the medication he customarily uses for his allergic difficulties. These should be clearly labeled so that the camp physician will know exactly what is being used. The child should also take with him to camp his own bedding, special pillows, blankets or blanket covers and mattress or mattress cover if necessary. Unless he rooms by himself, it will also be necessary to lend similar equipment to his camp mate.

The effect of swimming on the allergic condition is a problem to be judged in every individual case. Children with chronic atopic dermatitis (dry eczema) may swim. The lesions should be protected with petrolatum or some bland ointment. Since children with eczematous skins are ordinarily quite sensitive to light, care should be taken to avoid sunburn, and a coat of tan should be acquired very gradually. If tar ointments are used, the skin is particularly sensitized to light, and either special care must be used or an ointment not containing tar should be substituted.

In general, the allergic child should avoid animals in camp as well as at home. In crafts and hobbies taught in camp he should avoid the preparing and mounting of animals with fur or feathers. It is better to interest the child in mineralogy or geology or the study of fossils or fish. He should not go on overnight hikes where he might have to sleep on the ground or in a barn. He should be taught to avoid poison ivy, and, should he be sensitive to this, prophylactic measures should be instituted before he goes to camp. Abnormally severe reactions to insect stings may occur, and if this happens the nature of the insect should be determined so that specific prophylactic therapy may be given if necessary.

AUTHOR'S ABSTRACT.

ANTIREAGIN IN THE DESENSITIZATION OF PATIENTS WITH ALLERGIC DISEASES. S. P. KLEIN and H. A. E. VAN DISHOECK, Nederl. tijdschr. v. geneesk. **86:** 2699 (Oct. 31) 1942.

With the desensitization of allergic patients the circulating as well as the non-circulating regimen always was increased by administration of small doses. When large doses were given a blocking substance was formed which Cooke could demonstrate in patients with hay fever. This same substance proved also to be present in other cases of inhalant and food allergies, except in allergy to house dust. The blocking substance has no effect on the cell or the allergen, but combined with the reagin it has already an effect in vitro. The name "antireagin" therefore is justified. The antireagin is usually present in the serum in excessive quantities and is able to bind a certain quantity of added reagins. In this way the quantity of antireagin can be determined (blocking index). The antireagin is not individually specific, so that the serum of the treated patient can have a retarding effect on an untreated patient. The antireagin as well as the reagin is specific in respect to allergens; thus antireagins for pollen do not have a retarding effect on allergy to feathers or house dust. The recovery of the patient as the result of desensitization with large doses (more than 25,000 units of pollen per treatment) is most probably caused by the formation of antireagin. Favorable results obtained with small doses are on the contrary perhaps the result of an increase of reagin.

VAN CREVELD, Amsterdam, Netherlands.

PSORIASIS IN TIME OF WAR. J. R. PRAKKEN, Nederl. tijdschr. v. geneesk. **86:**3037 (Dec. 5) 1942.

In 53 out of 99 causes of psoriasis in which treatment was given between March and October 1942, exacerbations were seen, notwithstanding the low fat ration. This fact may be used as an argument against the theory of Grütz and Bürger (1933).

VAN CREVELD, Amsterdam, Netherlands.

Miscellaneous

OXYGEN TOXICITY: THE EFFECT OF INHALATIONS OF HIGH CONCENTRATIONS OF OXYGEN FOR TWENTY-FOUR HOURS ON NORMAL MEN AT SEA LEVEL AND AT A SIMULATED ALTITUDE OF 18,000 FEET. JULIUS H. COMROE JR., ROBERT DRIPPS, PAUL DUMKE and MARGO DEMING, J. A. M. A. **128**:710 (July 7) 1945.

Inhalation of 100 per cent oxygen over a twenty-four hour period caused substernal distress in 82 per cent of the normal subjects. The incidence was not decreased by intermittence of administration—up to fifteen minutes rest every three hours. Inhalation of 100 per cent oxygen at high altitudes caused no symptoms. This indicates that symptoms are due to high oxygen tension rather than to elimination of nitrogen. Seventy-five per cent oxygen caused symptoms in 55 per cent of the subjects and 50 per cent oxygen in none of the subjects. "Since oxygen tents or catheters rarely produce alveolar oxygen concentrations higher than 50 per cent, these forms of administering oxygen are completely safe." The use of 100 per cent oxygen over periods longer than twelve hours requires special precautions.

BAIRD, Wauwatosa, Wis.

BORIC ACID: A DANGEROUS DRUG OF LITTLE VALUE. E. H. WATSON, J. A. M. A. **129**:332 (Sept. 29) 1945.

Fatal boric acid poisoning occurred in a 4½ month old white boy with severe generalized infantile eczema, when compressing of the entire body with saturated boric acid solution was followed by the twice daily application of boric acid ointment U. S. P. Early symptoms were fever, convulsions and an intense erythema of the skin. "The medical profession as a whole probably puts unwarranted confidence in boric acid preparations and is likely to forget that boric acid is a poison."

BAIRD, Wauwatosa, Wis.

PSEUDODOXIA PEDIATRICA. HARRY BAKWIN, New England J. Med. **232**:691 (June 14) 1945.

It is the author's purpose in this paper to inquire into some of the current pediatric errors and to analyze the reasons why they persist. One recalls how only a few years ago babies' mouths were meticulously cleansed, presumably to remove germs, and how the symmetric ulcers of the palate, still occasionally seen, resulted. Even more recent was the discovery that liquid petrolatum, dropped into the nose, almost a routine procedure among well-cared-for babies a few years ago, may lead to pneumonia. One may mention here also the vigorous removal of the vernix caseosa as an etiologic factor in impetigo of the newborn. It is known that overrigid feeding schedules fostered parental overanxiety and frequently led to anorexia in young children.

Prominent among these unwise practices is indiscriminate tonsillectomy. Attention may be called to the facts that mortality from the operation is by no means negligible, about 80 persons dying each year in the United States as a result of the anesthesia administered for this operation and an equal number in England, where chloroform is widely used; that the morbidity from pneumonia, pulmonary abscess, hemorrhage and sepsis is considerable; that the etiologic relation of tonsillectomy to bulbar poliomyelitis is well established, and that the operation may be an exciting factor in the anxiety neurosis of children.

Until the introduction of the sulfonamide drugs it was not unusual for the large majority of infants in a hospital ward to have purulent otitis media during the winter months. The high incidence of myringotomy was by no means limited to hospitals. In home practice, too the ear drums were and still are too freely incised.

During recent years in America there has been a rapid increase in the percentage of hospital deliveries. In New York city, for example, 97.3 per cent of all

births took place in hospitals during 1943, in comparison with 61.9 per cent in 1929, an increase of over 50 per cent in less than fifteen years. There are, however, no data indicating that indiscriminate hospitalization for delivery has had a favorable influence on either maternal or neonatal mortality. Hospitals are unsuited for the care of the newborn. Physicians and parents who would hesitate to permit older infants in a hospital ward seem to have no qualms about having newborn babies there, even though obstetric nurseries are generally more crowded than in the usual infant ward. Fortunately, the newborn are resistant to many of the common infections that beset older infants. The immunity of the newborn is, however, limited, as is evidenced by the frequency with which diarrhea, pneumonia, sepsis and other infections occur among them. These conditions are rare in the home, and babies kept there are obviously not exposed to nursery epidemics. The number of deaths from diarrhea of the newborn is not inconsiderable. During the ten year period 1934 through 1943, 669 infants died of this condition in New York city. A great drawback in the hospital is the separation of mother and baby. This is unnatural and unphysiologic. Certainly among mammals it is the rule that the young remain in close contact with the mother during early life, snuggling against her.

Whereas the hospital facilitates the work of the obstetrician, it hampers that of the pediatrician, especially in the handling of private patients. The obstetric hospital is in good part responsible for the failure of many mothers to feed their babies at the breast. The pediatrician is generally called in several days after delivery, during which time no effort has been made to initiate breast feeding. Instead, a formula has been prescribed, and this, since it satisfies the appetite, discourages the baby from sucking the breast, thereby removing the stimulus for secretion of milk. That the hospital is the proper place for the delivery of selected patients when difficulties are anticipated is apparent. But some modification of the present system of indiscriminate hospital delivery is indicated.

Although pediatricians have shown an increasing interest in the psychologic care of the child, they still underestimate its importance or are unwilling to make the effort necessary to inform themselves about it. Pediatrics of the recent past was dominated to a large extent by a mechanistic viewpoint toward child rearing, and little or no attention was paid to emotional and spiritual needs.

It is unusual nowadays to see a new patient who is not receiving vitamin supplements, yet there is no definite clinical evidence that deficiency diseases are at all widespread among children or that any benefit can be derived from the general use of vitamins, except in the case of vitamins C and D in infancy. There are numerous other erroneous practices. Such are the unnecessary treatment of physiologic bowing of the legs; the premature use of orthodontia, and the diagnosis and treatment of rickets because the ribs flare or the legs are bowed or the shape of the head is unusual, although rickets is not the cause.

A major error in pediatric education is the failure to prepare students properly for practice in the home.

GENGENBACH, Denver.

SOME ASPECTS OF INFANTILE PATHOLOGY IN THE CITIES OF THE WESTERN NETHERLANDS DURING THE TIME OF THE BLOCKADE. A. MIDDELHOVEN, Ann. pædiat. **165**:225 (Nov.) 1945.

The author gives an account of the serious consequences of the hunger blockade of the Western Netherlands, with respect to the development, the morbidity and the mortality of infants. Special attention is given to the excessively low temperatures observed and to nutritional disturbances. A large number of dystrophic children fell victim to a mysterious contagious enteric disease which proved to be responsible for a number of cases of toxicosis as well.

Numerous case histories are included in the article.

AUTHOR'S ABSTRACT.

Book Reviews

Recent Advances in Obstetrics and Gynecology. By Aleck W. Bourne, M.B., B.Ch., and Leslie H. Williams, B.S. Sixth edition. Price, $5.50. Pp. 357, with 77 illustrations. Philadelphia: The Blakiston Company, 1945.

This little book by two British authors, which may be compared to one of the series of "Year Books" which have appeared in this country for many years, is a brief review of the literature for the past few years. The authors are both men of experience, and both hold responsible positions in London hospitals. A book of this size cannot treat all phases of the large field which it covers, but most of the questions concerning which there has been difference of opinion or the development of new information are discussed. The literature has evidently been well reviewed, and the writers have by no means limited themselves to the work of their fellow countrymen, for much American, Continental and Canadian work is mentioned. The selection of material and the method of handling it may be commended. An excellent chapter on recent work in obstetric analgesia and anesthesia is given, although one may not share the authors' rather favorable opinion of chloroform. The subject is ably dealt with, and one may commend the conclusion that spinal anesthesia is not advisable for cesarean section. There is an excellent discussion of obstetric radiology and a brief but satisfying exposition of the present state of knowledge concerning erythroblastosis.

The chapters on cancer of the uterus and of the ovary are adequate. Extracts from the literature are judicious, and the comments are illuminating. Radiotherapy is well discussed, and a comparative evaluation of the merits of radiologic and surgical therapy of carcinoma of the cervix is provided.

Recent methods in the management of sterility are reviewed. The proportion of cases of barrenness due to male sterility seems less than is found in most clinics in this country, but the chapter gives a good idea of present day methods.

Nearly all books which deal with gynecology attempt a classification of ovarian tumors, and this one is no exception. The classification given is perhaps as good as any, although none has so far been wholly satisfying. A good discussion of the pathology, histogenesis and treatment of tumors is given.

The book may be commended as a brief but accurate review of the literature, and it will be useful to any one wishing to go over quickly the more important evidences of progress in the last two or three years.

Familial Nonreaginic Food-Allergy. Second edition. By Arthur F. Coca, M.D. Price, $3.75. Pp. 191, with 28 tables and 14 charts. Springfield, Ill.: Charles C Thomas, Publisher, 1945.

Whenever an entirely new concept at variance with current practice is presented to the medical profession, it is usually received with skepticism. Often some such concepts obtain a few adherents and flourish for a while, soon to be discarded; others are found to be sound and are added to the permanent material of the medical structure. Time will tell to which category the substance of this book belongs.

Dr. Coca has brought forward an entirely new view of many ailments, which will not be readily accepted by allergists or by the medical profession at large. His high professional standing and the worth of his many previous contributions to allergy, however, demand that anything he writes be given serious consideration.

Nonreaginic familial food allergy, or "idioblaptic" (from the Greek, meaning "individual spoiler") allergy, as Dr. Coca has called it, affects a large proportion of the human race. It is likely to be multiple; one patient whom he studied was

sensitive to all foods except beef. In a series of 210 unselected persons, only 41 were found to be free from this allergy. The allergic reaction is commonly to foods, but it may be to animal danders, or to other emanations, such as tobacco smoke and automobile exhaust fumes, or to inorganic substances, such as metals.

The eleven commonest symptoms of "idioblaptic" allergy are headache, tiredness, nervousness, indigestion, dizziness, constipation, neuralgia, canker sores, chronic rhinitis and urticaria. Hypertension, epilepsy, pain in the chest, angina pectoris, dysmenorrhea, frequent epistaxes and many other diseases and symptoms may be caused by it. Fifty patients with dementia precox had it, as did 297 women with malignant tumors of the breast; and if it is not the actual cause of these conditions, it is at least an important predisposing factor.

In "idioblaptic" allergy the specific allergen causes an acceleration of the pulse rate, and the allergens involved are determined by examination of the pulse before and after the suspected food is eaten. No antibodies have been demonstrated, and cutaneous tests elicit negative reactions. The daily range of the normal pulse rate from low to high is rarely more than 16 beats per minute. The daily maximum does not vary more than 2 beats per minute. "If, then, the daily range of the pulse rate exceeds 20, and if the daily maximal counts per minute vary more than 2 beats, the patient is practically certainly affected with idioblaptic allergy."

The reviewer gets the impression that "idioblaptic" allergy is a powerful and far reaching ailment. If 75 per cent of the population cannot eat their victuals, this is indeed to be deplored. "Most of the misery of human existence is due to it."

Strong stuff surely, and hard to swallow! If any one else but Dr. Coca had written this book, the reviewer would not even attempt to swallow it and would be willing to express the opinion that there is little virtue in it. Having, however, a high opinion of the author, he suggests that his very radical and somewhat fantastic ideas be not condemned by the members of the medical profession until some time has passed. If the concept of "idioblaptic" allergy is sound, it will not be long before others will duplicate the results that Dr. Coca has obtained, although it is inconceivable that this disorder should be at the root of so many ailments as he believes. If they cannot be duplicated, it will go the way that so many methods of treatment in medicine have gone during the last thousand years.

Essentials of Clinical Allergy. By Samuel J. Taub, M.D., Professor of Medicine, Cook County Graduate School of Medicine. Price, $3.00. Pp. 198, with 16 plates. Baltimore: The Williams and Wilkins Company, 1945.

This volume, appearing from the press of the Williams and Wilkins Company, is well printed and of good format.

The author has attempted to write an extremely short treatise on clinical allergy, which is a commendable effort. Unfortunately for a book of this size, the material has not been well enough digested. The first part, covering the underlying principles of allergy, fails in its purpose because it does not give an adequate over-all picture of the immunology, chemistry, pathology and physiology necessary for a good working basis, particularly for a student untrained in the field of allergy. Many inaccuracies are present, and the author fails to note the existence of moot questions.

The chapters on hay fever are perhaps the best and present a rather good description of the study and management of this problem. One might take exception to the large doses advocated for treatment, for too many constitutional reactions must result from such an approach.

The remaining chapters give a kaleidoscopic view of the author's impressions of other allergic syndromes. Again, this reviewer must state with pain that these chapters too can afford little help for the untrained worker in this field.

For the pediatrician, this volume offers little help in the solution of the problems of allergy found in children.

As an extremely short story about the subject of allergy, Dr. Taub's book may perhaps serve some purpose. There are other short volumes on this subject,

however, which in the opinion of this reviewer are far superior. One cannot but remark that the subject matter does not equal the fine job done by the publishers.

Lehrbuch der allgemeinen Kinderpsychiatrie einschliesslich der allgemeinen Psychiatrie der Pubertät und Adoleszenz. By M. Tramer, Privat-dozent der Universitaet Bern; Direktor der kantonalen Heilanstalt Rosegg, Solothurn, etc. Zweite Auflage. Price, Fr. 32. Basel, Switzerland: Benno Schwabe, 1945.

The appearance of a second edition of this text is ample evidence of the success of the author's original attempt, and success it deserved. The reviewer knows of no other volume which so thoroughly covers the field of child psychiatry.

In the present edition many of the chapters have been enlarged. Among the material which is new in the second edition are discussions of "Onychophagy"—finger nail biting—and "The Only Child."

The reviewer has read both editions of this textbook with a great deal of interest. He was impressed with the philosophy underlying the explanation of many of the problems and the conflicts of the young organism and its struggle for a place in a society of grownups. That simple, everyday behavior problems, which the pediatrician sees by the score every month—problems which in the huge majority of the cases solve themselves in due course of time—should be so complex and full of profound psychic disturbances is just too difficult to grasp. However, the reviewer is only a pediatrician.

Men Without Guns. By DeWitt Mackenzie. Descriptive Captions by Clarence Worden; Foreword by Norman T. Kirk. Price, $5.00. Pp. 48, with 137 plates from the Abbott collection of paintings owned by the U. S. Government. Philadelphia: The Blakiston Company, 1945.

This volume contains an account by an eye witness of what has happened on the various fronts in the Medical Corps of the United States Army. It is interesting to note that the text consists largely of statements made by artists who were sent at the expense of the Abbott Laboratories to depict the work of this excellent branch of the Army. That these artists speak with such uniform praise of the Army Medical Corps—the doctors, nurses and corpsmen—is a tribute to American manhood and womanhood.

Each, in turn, has emphasized the thing he has encountered in his work. Each has praised without stint the labor of the corpsmen, the devotion to duty of the doctors and nurses and the indefatigable work of the entire Corps.

Each theater of operation is described in separate chapters by different artists. The nature of the report is explicitly the same.

The last chapter is one on the rehabilitation of the men in service, and in it are some apt instructions to people at home. The Surgeon General says, among other things: "The wounded soldier does not want sympathy; neither does he want charity."

At the end of the book there are various paintings depicting vividly the work of the Medical Corps on one front after another. The artist has taken the outstanding scenes and has depicted them as only an artist can.

The illustrations are most interesting and extremely well done, and the book is beautifully bound and illustrated.

Directory of Pediatric Societies *

INTERNATIONAL

International Association of Preventive Pediatrics

President: Prof. S. Monrad, Dronning Louises Børnehospital, Copenhagen, Denmark.
Secretary: Dr. Daniel Oltramare, 15 Rue Lévrier, Geneva, Switzerland.

International Congress of Pediatrics

President: Dr. Henry F. Helmholz, Mayo Clinic, Rochester, Minn.
Secretary-General: Dr. L. Emmett Holt Jr., 477 First Ave., New York 16.
Canadian Committee:
Chairman: Dr. Alan Brown, Hospital for Sick Children, 67 College St., Toronto 2.
Secretary: Dr. H. P. Wright, 1414 Drummond St., Montreal.
Place: New York. Time: Sept. 16-19, 1947.

International Congress for the Protection of Infancy

Secretary: Prof. G. B. Allaria, Corso Bramante 29, Torino 120, Italy.

Save the Children International Union

President: Mrs. Gordon Morier.
Secretary: Dr. Georges Thélin, 43 Quai Wilson, Geneva, Switzerland.
Place: Geneva, Switzerland. Time: Sept. 17-20, 1946.

FOREIGN

Argentine Pediatric Society of Buenos Aires

President: Dr. Martin Ramón Arana, 1809 Rodriguez Peña, Buenos Aires.
General Secretary: Dr. Alfredo Larguia, Cerrito 1179, Buenos Aires.

Associação Paulista de Medicina, Secção de Pediatrias

President: Dr. Vicente Lara.
First Secretary: Dr. Armando de Arruda Sampaio.
Second Secretary: Dr. Luiz Augusto Monteiro Toledo, Av. Brigadeiro Luiz Antonio 393, 1° Andar, São Paulo, Brazil.
Time: Twelfth of every month, 8:30 p. m.

British Paediatric Association

President: Prof. G. B. Fleming, 13 Lynedoch Crescent, Glasgow.
Joint Secretary: Prof. Alan Moncrieff and Dr. Donald Paterson, Hospital for Sick Children, Great Ormond St., London, W. 1.
Place: Rugby School, Rugby. Time: Aug. 1-3, 1946.

Danish Pediatric Society

President: Dr. E. Lenstrup, Copenhagen.
Secretary: Dr. Gjørup, Dronning Louises Børnehospital, Copenhagen.

Nederlandische Vereeniging voor Kindergeneeskunde

President: Dr. J. H. G. Carstens, Servaas Bolwerk 14, Utrecht.
Secretary: Dr. R. P. van de Kasteele, Lyccumplein 10, den Haag.
Place: Children's Hospital or Pediatric Clinic. Time: Three times a year.

* Secretaries of societies are requested to furnish the information necessary to make this list complete and to keep it up to date.

PALESTINE JEWISH MEDICAL ASSOCIATION, SECTION OF PHYSICIANS OF CHILDREN'S DISEASES

President: Prof. L. F. Meyer, 29 Toelsohn St., Tel Aviv.
Secretary: Dr. A. Brünn, 9 Maazestre, Tel Aviv.

ROYAL SOCIETY OF MEDICINE, SECTION FOR THE STUDY OF DISEASE IN CHILDREN

President: Prof. Norman Capon, 49A Rodney St., Liverpool, England.
Secretary: Dr. J. N. O'Reilly, 46 Harley St., London, W. 1, England.
Place: 1 Wimpole St., London. Time: Fourth Friday of each month, 4:15 p. m.

SOCIEDAD CUBANA DE PEDIATRIA

President: Dr. Teodosio Valledor, Habana.
Secretary: Dr. Carlos Hernandez Miyares, Hospital Nuestra Señora de las Mercedes L y 21, Apartado, 2430, Habana.
Place: Cátedra de Clínica Infantil, Hospital Nuestra Señora de las Mercedes y Hospital Municipal de Infancia, Habana. Time: Last Wednesday of every month.

SOCIEDAD ECUADORIANA DE PEDIATRIA

President: Dr. Francisco de Icaza Bustamente.
Secretary: Dr. M. I. Gómez Lince, P. O. Box 693, Guayaquil.

SOCIEDAD MEXICANA DE PEDIATRIA

President: Dr. Fernando López Clares, 12/a. Medellín 191, Mexico.
Secretary: Dr. Jesus Gómez Pagola, Versalles 64, Mexico.

SOCIEDAD DE PEDIATRIA DE CÓRDOBA

President: Dr. Juan Francisco Herrera, Córdoba, Argentina.
Secretary: Dr. Bernardo Serebrinsky, Dean Funes 2000, Esq. Ocaña (N.), Córdoba, Argentina.
Place: Comite pro Defenso del Niño, Dean Funes 2000, Córdoba, Argentina. Time: Once a month.

SOCIEDAD DE PEDIATRÍA DE SANTIAGO DE CUBA

President: Dr. Antonio Béguez César, Sagarra 107, Santiago de Cuba.
Secretary: Dra. Susana Texdó Vaillant, Padre Pico 57, Santiago de Cuba.
Place: Colegio Médico. Time: Last Tuesday of every month.

SOCIEDAD VENEZOLANA DE PUERICULTURA Y PEDIATRIA

President: Dr. Pedro J. Alvarez.
Secretary: Dr. Ernesto R. Figueroa, 3a Avenida 10, Bella Vista, Caracas.
Place: Hospital Municipal de Niños Jose Manuel de los Rios, Caracas.

SOCIÉTÉ DE PÉDIATRIE DE PARIS

President: Dr. Leveuf, Paris, France.
Secretary: Dr. Jean Hallé, 10 bis Rue Pré aux Clercs, Paris, France.
Place: Hôpital des Enfants Maladies, 149 Rue de Sèvres. Time: 4:30 p. m., third Thursday of every month.

SWEDISH MEDICAL SOCIETY, SECTION FOR PEDIATRICS AND SCHOOL HYGIENE

President: Prof. Arvid Wallgren, 53 Strandvägen, Stockholm.
Secretary: Dr. Henning Magnusson, 58 Odengatan, Stockholm.
Place: Various clinics and hospitals in Stockholm and Uppsala. Time: Second Friday of each month (except summer).

URUGUAYAN SOCIETY OF PEDIATRICS

President: Dr. Jose Bonaba, Montevideo.
Secretary: Dr. Héctor Fossatti, Durazno 1882, Montevideo.
Place: Club Medico del Uruguay, Avenida Agraciado 1464 (Piso 13), Montevideo.

NATIONAL

American Medical Association, Scientific Assembly, Section on Pediatrics

Chairman: Dr. John Aikman, 184 Alexander St., Rochester, N. Y.
Secretary: Dr. Gilbert J. Levy, 188 S. Bellevue Blvd., Memphis, Tenn.

American Academy of Pediatrics

President: Dr. Jay I. Durand, 515 Cobb Bldg., Seattle, Wash.
Secretary: Dr. Clifford G. Grulee, 636 Church St., Evanston, Ill.
Place: Hotel William Penn, Pittsburgh. Time: Nov. 13-16, 1946.

American Hospital Association, Massachusetts Hospital Association

Chairman: Dr. Mr. Frank Wing, Boston.
Secretary: Dr. W. Franklin Wood, McLean Hospital, Waverly 79, Mass.
Place: Boston. Time: November 1946.

American Pediatric Society

President: Dr. Harold K. Faber, 2361 Clay St., San Francisco.
Secretary-Treasurer: Dr. Henry G. Poncher, 1819 W. Polk St., Chicago 12.

Canadian Society for the Study of Diseases of Children

President: Dr. H. S. Little, 300 Dufferin Ave., London, Ontario.
Secretary-Treasurer: Dr. Elizabeth Chant Robertson, 67 College St., Toronto 2.
Place: Banff, Alberta. Time: June 14-15, 1946.

Society for Pediatric Research

President: Dr. Mitchell I. Rubin, 219 Bryant St., Buffalo 9, N. Y.
Secretary: Dr. Robert F. Ward, Bellevue Hospital, New York 16.

SECTIONAL

Intermountain Pediatric Society

President: Dr. Robert Alway, University of Utah School of Medicine, Salt Lake City 2.
Secretary-Treasurer: Dr. L. Paul Rasmussen, 1020 Boston Bldg., Salt Lake City 1.
Place: Salt Lake City General Hospital. Time: First Thursday of each month, 8 p. m.

New England Pediatric Society

President: Dr. James Marvin Baty, 1101 Beacon St., Brookline, Mass.
Secretary-Treasurer: Dr. Charles D. May, 300 Longwood Ave., Boston.
Place: Boston Medical Library. Time: Three meetings a year, occurring from September to May.

North Pacific Pediatric Society

President: Dr. Percy Guy, 502–2d Ave., Seattle, Wash.
Secretary: Dr. Aldis B. Johnson, 515 Cobb Bldg., Seattle, Wash.
Place: Vancouver, B. C. Time: Oct. 19, 1946.

Northwestern Pediatric Society

President: Dr. George B. Logan, 102 Second Ave. S. W., Rochester, Minn.
Secretary-Treasurer: Dr. Northrop Beach, 1009 Nicollet Ave., Minneapolis.
Place: Minneapolis, St. Paul, Duluth and Rochester. Time: January, April, July and October.

ROCKY MOUNTAIN PEDIATRIC SOCIETY

President: Dr. G. R. Fisher, 23 E. Pikes Peak Ave., Colorado Springs, Colo.
Secretary: Dr. Joseph H. Lyday, 1850 Gilpin St., Denver 2.

SOUTHERN MEDICAL ASSOCIATION, SECTION OF PEDIATRICS

Chairman: Dr. William Weston Jr., 1428 Lady St., Columbia, S. C.
Secretary: Dr. Angus McBryde, 604 W. Chapel Hill St., Durham, N. C.

STATE

ALABAMA PEDIATRIC SOCIETY

President: Dr. Jerome C. Chapman, 2160 Highland Ave., Birmingham.
Secretary-Treasurer: Dr. Ruth Berrey, 2021–6th Ave. N., Birmingham.
Place: Birmingham. Time: September 1946.

ARIZONA PEDIATRIC SOCIETY

President: Dr. Vivian Tappan, San Clemente, Tucson.
Secretary: Dr. Hilda Kroeger, Arizona State Health Dept. (Maternal and Child Welfare Division), Phoenix.
Place: Phoenix or Tucson. Time: At time of state meeting.

ARKANSAS STATE PEDIATRIC ASSOCIATION

Chairman: Dr. C. B. Billingsley, 1425 N. 11th St., Fort Smith.
Secretary: Dr. R. E. Weddington, 1425 N. 11th St., Fort Smith.

CALIFORNIA STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

Chairman: Dr. Charles W. Leach, 2000 Van Ness Ave., San Francisco 9.
Secretary: Dr. Chester I. Mead, 1930 Truxton Ave., Bakersfield.
Place: Biltmore Hotel, Los Angeles. Time: May 7-10, 1946.

FLORIDA STATE PEDIATRIC SOCIETY

President: Dr. Councill Rudolph, 103–5th St. S., St. Petersburg.
Secretary: Dr. Robert Blessing, 409 Blount Bldg., Ft. Lauderdale.
Place: Concurrent with state association convention and fall meeting.

GEORGIA PEDIATRIC SOCIETY

President: Dr. Alton Johnson, 102 E. Central Ave., Valdosta.
Secretary-Treasurer: Dr. Don F. Cathcart, 478 Peachtree St. N. E., Atlanta.
Place: Atlanta. Time: At time of annual state meeting.

HEZEKIAH BEARDSLEY PEDIATRIC CLUB OF CONNECTICUT

President: Dr. Edward T. Wakeman, 129 Whitney Ave., New Haven.
Secretary: Dr. Herman Yannet, Southbury Training School, Southbury.
Place: New Haven. Time: September 1946.

ILLINOIS STATE MEDICAL SOCIETY, SECTION ON PEDIATRICS

Chairman: Dr. Craig D. Butler, 715 Lake St., Oak Park.
Secretary: Dr. A. J. Fletcher, 139 N. Vermilion, Danville.

INDIANA STATE PEDIATRIC SOCIETY

President: Dr. K. T. Knode, 1105 E. Jefferson Bldg., South Bend.
Secretary-Treasurer: Dr. Matthew Winters, 621 Hume Mansur Bldg., Indianapolis.
Time: Two meetings a year.

IOWA PEDIATRIC SOCIETY

President: Dr. Arnold M. Smythe, 406–6th Ave., Des Moines.
Secretary-Treasurer: Dr. James Dunn, 414 Blackhawk Hotel, Davenport.
Place: Des Moines. Time: April 18, 1946.

LOUISIANA STATE PEDIATRIC SOCIETY

President: Dr. S. George Wolfe, 1560 Line Ave., Shreveport.
Secretary-Treasurer: Dr. W. C. Rivenbark, 1448 Louisiana Ave., New Orleans 15.

MEDICAL SOCIETY OF STATE OF NEW YORK, SECTION ON PEDIATRICS

Chairman: Dr. Carl H. Laws, 12 Pierrepont St., Brooklyn, N. Y.
Secretary: Dr. George R. Murphy, 292 Madison Ave., New York.
Place: Hotel Pennsylvania, New York. Time: May 2-3, 1946.

MEDICAL SOCIETY OF THE STATE OF PENNSYLVANIA, PEDIATRIC SECTION

Chairman: Dr. Elwood W. Stitzel, 403 Central Trust Bldg., Altoona, Pa.
Secretary: Dr. P. F. Lucchesi, Philadelphia Hospital, Philadelphia.

MICHIGAN STATE MEDICAL SOCIETY, PEDIATRIC SECTION

Chairman: Dr. Donald J. Barnes, 3001 W. Grand Blvd., Detroit, Mich.
Secretary: Dr. Mark F. Osterlin, Central Michigan Children's Clinic, Traverse City.
Place: Detroit. Time: Sept. 25-27, 1945.

MISSISSIPPI STATE PEDIATRIC SOCIETY

President: Dr. Harvey F. Garrison Jr., 315 E. Capitol Pl., Jackson.
Secretary: Dr. Guy Verner, 126 N. Congress St., Jackson.

NEBRASKA PEDIATRIC SOCIETY

President: Dr. John M. Thomas, 1418 Medical Arts Bldg., Omaha 2.
Secretary-Treasurer: Dr. Gerald C. O'Neil, 640 City National Bank Bldg., Omaha.
Place: As announced by committee. Time: Third Thursday of each month from October to June, inclusive. Dinner at 6 p. m.

NEW MEXICO STATE PEDIATRIC SOCIETY

President: Dr. M. K. Wylder, 221 W. Central Ave., Albuquerque.
Secretary-Treasurer: Dr. Ly Werner, 221 W. Central Ave., Albuquerque.

NORTH CAROLINA PEDIATRIC SOCIETY

President: Dr. Charles R. Bugg, Profesional Bldg., Raleigh.
Secretary: Dr. Charles F. Williams, 817 Hillsboro St., Raleigh.
Place: Roaring Gap. Time: September 1946.

NORTHERN CALIFORNIA PEDIATRIC SOCIETY

President: Dr. Edith M. Meyers, 431–30th St., Oakland.
Secretary: Dr. A. L. Gleason, 411–29th St., Oakland 9.
Place: San Francisco. Time: Second Thursday of February, April, September and November.

OKLAHOMA STATE PEDIATRIC SOCIETY

President: Dr. G. R. Russell, 604 S. Cincinnati Ave., Tulsa.
Secretary: Dr. Luverne Hays, 108 W. 6th St., Tulsa.
Place: With Oklahoma State Medical Association. Time: Annual Meeting.

SOUTH CAROLINA PEDIATRIC SOCIETY

President: Dr. George D. Johnson, Spartanburg.
Secretary-Treasurer: Dr. B. O. Ravenel, Roper Hospital, Charleston:

Texas Pediatric Society

President: Dr. Max Woodward, 202 N. Travis St., Sherman.
Secretary-Treasurer: Dr. John E. Ashby, 3610 Fairmount Ave., Dallas 4.
Place: Fort Worth. Time: Oct. 4-5, 1946.

Virginia Pediatric Society

President: Dr. Emily Gardner, 1100 W. Franklin St., Richmond 20.
Secretary: Dr. Louise Galvin, 214 S. Boulevard, Richmond 21.

West Virginia State Medical Society, Section on Pediatrics

President: Dr. Jack Basman, 1021 Quarrier St., Charleston.
Secretary: Dr. Harry E. Baldock, Medical Arts Bldg., Charleston.
Place: Huntington. Time: May 13-15, 1946.

LOCAL

Academy of Medicine of Cleveland, Pediatric Section

Chairman: Dr. J. I. Hartman, 10515 Carnegie Ave., Cleveland.
Secretary: Dr. Alexander N. Freed, 2012 W. 25th St., Cleveland.
Place: Cleveland Medical Library Bldg. Time: 8:15 p. m., October, December, February and April.

Academy of Medicine, Toronto, Section of Pediatrics

President: Dr. J. H. Ebbs, 13 Queen's Park, Toronto, Canada.
Secretary: Dr. J. F. McCreary, 170 St. George St., Toronto, Canada.
Place: Academy of Medicine. Time: 8:30 p. m., third Thursday of each month.

Bronx Pediatric Society

President: Dr. Walter Levy, 12 E. 88th St., New York.
Secretary: Dr. Joseph Blasenstein, 960 Grand Concourse, New York.
Place: Concourse Plaza Hotel, 161st St. and Grand Concourse. Time: Second Wednesday of each month, except June, July, August and September.

Brooklyn Academy of Pediatrics

President: Dr. Lambert Krahulik, 14 Sidney Pl., Brooklyn.
Secretary: Dr. Joseph Battaglia, 713 Bushwick Ave., Brooklyn 21.
Place: Granada Hotel. Time: 8:45 p. m. fourth Wednesday of February, March, April, May and November.

Buffalo Pediatric Society

President: Dr. Douglas P. Arnold, 159 Bidwell Parkway, Buffalo, N. Y.
Secretary: Dr. Richard A. Downey, 786 Forest Ave., Buffalo 9, N. Y.
Place: Children's Hospital, 219 Bryant St. Time: 8:30 p. m., first Monday of each month from September to June.

Central New York Pediatric Club

President: Dr. Arthur W. Benson, 2 St. Paul St., Troy.
Secretary: Dr. Frank J. Williams, 58 S. Swan St., Albany.
Places: Various cities in New York. Time: Third Tuesday of April and October.

Chicago Pediatric Society

President: Dr. Louis W. Sauer, 636 Church St., Evanston, Ill.
Secretary: Dr. Henry G. Poncher, 1819 W. Polk St., Chicago 12.
Place: Children's Memorial Hospital, 710 Fullerton Ave. Time: Third Tuesday of each month, October to May inclusive.

Cincinnati Pediatric Society

President: Dr. Theodore K. Selkirk, 3605 Edwards Rd., Cincinnati.
Secretary: Dr. John H. Hunt, Kemper Lane Bldg., Cincinnati 6.
Place: Children's Hospital, Elland Ave., Cincinnati. Time: On call.

Dallas Pediatric Society

President: Dr. O. René Caillet, 4325 Cole Ave., Dallas, Texas.
Secretary-Treasurer: Dorothy Wyvell, Bradford Memorial Hospital for Babies, Texas.
Place: Children's Medical Center. Time: 1 p. m., third Saturday and 8:30 p. m. the first Thursday of each month.

Detroit Pediatric Society

President: Dr. Otto Grob, 651 Fisher Bldg., Detroit 2, Mich.
Secretary: Dr. Harold B. Rothbart, 773 Fisher Bldg., Detroit 2, Mich.
Place: Variable. Time: Third Wednesday of each month.

Houston Pediatric Society

President: Dr. Raymond Cohen, 2300 Caroline St., Houston, Texas.
Secretary: Dr. Betty Moody, 526 Richmond Rd., Houston, Texas.
Place: River Oaks Country Club. Time: 7:30 p. m., fourth Monday of each month.

Kansas City (Missouri) Pediatric Society

President: Dr. Harry M. Gilkey, 1624 Professional Bldg., Kansas City.
Secretary: Dr. Leland Speer, 1022 Parkway, Kansas City.
Place: Kansas City General Hospital. Time: On call.

Los Angeles County Medical Association, Pediatric Section

President: Dr. Milo B. Brooks, 1033 Gayley Ave. W., Los Angeles.
Secretary-Treasurer: Dr. Elena Boder, 1830½ Lucille Ave., Los Angeles 26.
Place: Los Angeles County Medical Headquarters, 1925 Wilshire Blvd. Time: Second Monday of February, April, June, October and December.

Medical Society of the County of Kings and the Academy of Medicine of Brooklyn, Pediatric Section

President: Dr. Henry Rascoff, 895 Eastern Parkway, Brooklyn.
Secretary: Dr. Harold Levy, 750 St. Marks Ave., Brooklyn.
Place: 1313 Bedford Ave., Brooklyn. Time: 9:00 p. m. fourth Monday of each month.

Medical Society of the County of Queens, Inc., Section on Pediatrics

Chairman: Dr. Meyeron Coe, 217-02-91st Ave., Queens Village, N. Y.
Secretary-Treasurer: Dr. Edith A. Mittell, 144-38th Ave., Flushing, N. Y.
Place: Queens County Medical Bldg., Forest Hills, N. Y. Time: Third Monday of October, January, March and May.

Medical Society of the District of Columbia, Section on Pediatrics

President: Dr. John Washington, 2203 Wyoming Ave., Washington, D. C.
Secretary-Treasurer: Dr. George Maksim, 1418 Good Hope Rd. S.E., Washington, D. C.
Place: Medical Society Bldg., 1718 M St. N. W. Time: 8 p. m., third Thursday of October, January, March and May.

Memphis Pediatric Society

President: Dr. Kinsey M. Buck, 1193 Madison Ave., Memphis, Tenn.
Secretary-Treasurer: Dr. Barton Etter, 1024 Madison Ave., Memphis, Tenn.
Place: Memphis Country Club. Time: 8 p. m., Dec. 13, 1946.

Milwaukee Pediatric Society

President: Dr. G. H. Fellman, 231 W. Wisconsin Ave., Milwaukee.
Secretary-Treasurer: Dr. R. P. Showalter, 411 E. Mason St., Milwaukee 2.
Place: Milwaukee Children's Hospital. Time: Second Wednesday in February, April, June, October and December.

New York Academy of Medicine, Section of Pediatrics

Chairman: Dr. Robert O. Du Bois, 122 E. 76th St., New York.
Secretary: Dr. Harold W. Dargeon, 1095 Park Ave., New York.
Place: New York Academy of Medicine, 2 E. 103d St. Time: Second Tuesday of each month from November to May, inclusive, 8:30 p. m.

Oklahoma City Pediatric Society

President: Dr. William M. Taylor, 625½ N. W. 10th St., Oklahoma City.
Secretary: Dr. Jeanne McKinnon-Shofstall, 1019 N. Lee St., Oklahoma City.
Place: Oklahoma Club. Time: Third Thursday of each month.

Philadelphia Pediatric Society

President: Dr. Waldo E. Nelson, Temple University School of Medicine, Philadelphia.
Secretary: Dr. Sherman Little, 1740 Bainbridge St., Philadelphia 46.
Place: College of Physicians, 19 S. 22d St. Time: 8:30 p. m., second Tuesday in October, December, February and April.

Pittsburgh Pediatric Society

President: Dr. Elwood Stitzel, 403 Central Trust Bldg., Altoona, Pa.
Secretary-Treasurer: Dr. C. J. Stoecklein, Medical Arts Bldg., Pittsburgh 13.
Place: Pittsburgh Academy of Medicine. Time: Second Friday in October, December, February and April.

Richmond Pediatric Society

President: Dr. Edwin L. Kendig Jr., 828 W. Franklin St., Richmond 20, Va.
Secretary-Treasurer: Dr. Thomas S. Chalkley, 1200 E. Broad St., Richmond, Va.
Place: Medical College Hospital. Time: 8 p. m., third Thursday of each month, except June, July and August.

Rochester Pediatric Society

President: Dr. William L. Bradford, 260 Crittenden Blvd., Rochester 7, N. Y.
Secretary-Treasurer: Dr. Donald D. Posson, 222 Chili Ave., Rochester 11, N. Y.
Place: Rochester Academy of Medicine or arrangement by program committee. Time: Third Friday of each month from October to May.

St. Louis Pediatric Society

President: Dr. Joseph C. Jaudon, 337 N. Euclid Ave., St. Louis.
Secretary-Treasurer: Dr. Gilbert B. Forbes, 500 S. Kingshighway, St. Louis 10.
Time: Second Thursday of each month from October to May, inclusive.

Seattle Pediatric Society

President: Dr. D. M. Dayton, 740 St. Helens Ave., Tacoma.
Secretary: Dr. W. B. Chesley, 1306 Madison St., Seattle 4.
Place: College Club. Time: Third Friday of each month from September to June at 6:30 p. m.

Southwestern Pediatric Society

President: Dr. Robert J. Dostal, 710 Wilshire Blvd., Santa Monica, Calif.
Secretary: Dr. H. M. Van Dyke, 541 E. Broadway, Long Beach, Calif.
Place: University Club of Los Angeles. Time: 6:30 p. m., first Wednesday in January, March, May, September and November.

University of Michigan Pediatric and Infectious Disease Society

President: Dr. Park Bradshaw, Muskegon, Mich.
Secretary: Dr. Harry A. Towsley, 1313 E. Ann St., Ann Arbor, Mich.
Place: University Hospital, Ann Arbor, Mich. Time: Oct. 25-26, 1946.

Westchester County Medical Society, Pediatrics Section (New York)

President: Dr. John B. Ahouse, 27 Ludlow St., Yonkers, N. Y.
Secretary-Treasurer: Dr. Elvira Ostlund, 64 Highland Rd., Rye, N. Y.
Place: Hospitals of Westchester County. Time: Third Thursday in November, January, March and May.